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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

MAY 1939

THE DIAGNOSTIC SIGNIFICANCE OF CHANGES IN THE RED CELLS*

RUSSELL L. HADEN

A NORMAL man always has about twenty-five trillion red cells in the circulating blood. The cells are remarkably uniform in size, shape, and hemoglobin content. All the erythrocytes together make up the erythron, which is best thought of as a vessel holding hemoglobin. The erythron normally varies little in volume since the number and size of the red cells and the total blood volume are quite constant. The characteristic biconcave shape of the erythrocyte is a most efficient one because it combines adequate capacity for containing hemoglobin with favorable conditions for the rapid diffusion of oxygen.

An adult male weighing 150 pounds has (Fig. 1):

1. A total blood volume of about 5 liters.
2. A total red cell mass or erythron of over 2 liters which holds about 700 gm. of hemoglobin.
3. Five million biconcave cells per c.mm.
4. A mean red cell volume of 90 cubic microns.
5. A mean cell hemoglobin content of 30.8 micromicrograms.
6. A mean cell hemoglobin concentration of 34.2 per cent.

* Delivered October 28, 1938 in the Eleventh Annual Graduate Fortnight.
From the Cleveland Clinic, Cleveland, Ohio.

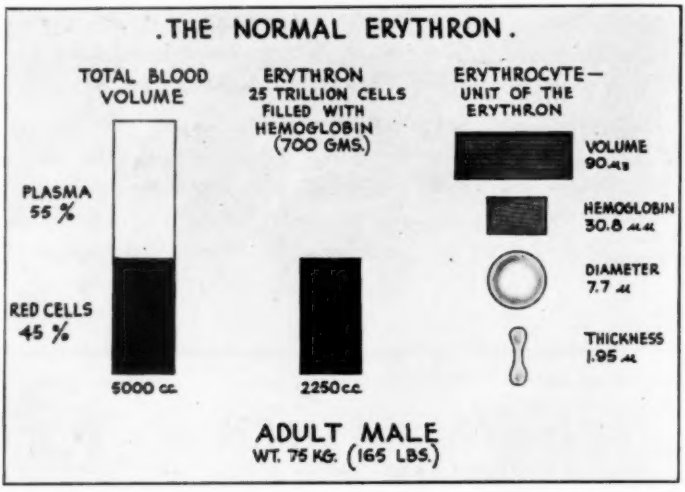


Fig. 1—The normal erythron. The erythron is the total mass of red cells. The unit of the erythron is the erythrocyte.

7. A mean cell diameter of 7.7 microns.
8. A mean cell thickness of 1.95 microns.

The cells normally in the circulation are mature as shown by the absence of nuclei and nuclear remains and by reticulation and basophilia in only a small percentage. The erythrocyte may vary in total mass, number, size, shape, hemoglobin content, and maturity.

The sole purpose of the red cell is to transport oxygen which it is enabled to do by reason of its hemoglobin content. Each cell is fully saturated or filled with hemoglobin and functions like a cup on an endless chain conveyor (Fig. 2). The hemoglobin is constantly taking up oxygen in the lungs and constantly releasing it in the tissues. The hemoglobin in the erythrocyte is really outside the blood plasma. It thus exerts no osmotic pressure and so does not disturb the normal balance between tissue fluids and plasma.

The total red cell mass or erythron has received little attention. Normally the total blood volume varies only in relation to body weight so the red cell mass calculated from the total blood volume and hematocrit reading is quite constant (males, 30 cc., females, 27 cc. per kg.).

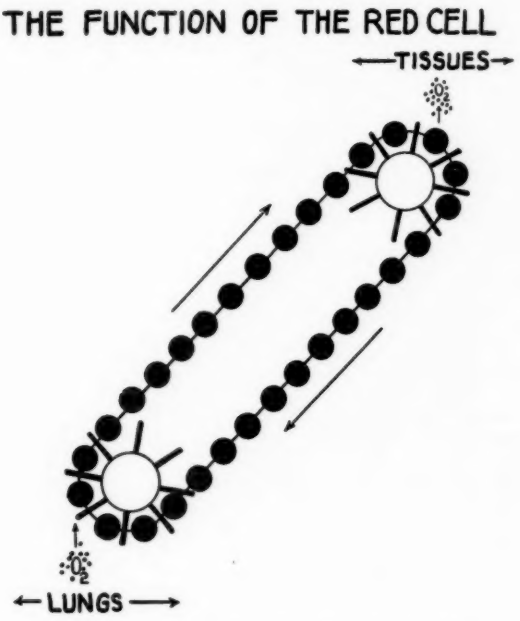


Fig. 2—The red cell functions as a cup on an endless chain conveyor. The cup (erythrocyte) is normally filled with hemoglobin which takes up oxygen in the lungs and gives it up in the tissues.

With an anemia the hematocrit value decreases (Fig. 3) while the total blood volume usually remains unchanged so the mass of erythron may fall to a very low level. The total blood volume is seldom significantly increased except in polycythemia vera where it is always greater than normal. The hematocrit value is also constantly increased in this condition, so the total red cell mass and the mass per kg. are always large. I have observed the volume of the erythron as high as 8000 cc. in polycythemia vera and as low as 400 cc. in aplastic anemia (normal 2000-2500 cc.). The determination of the total red cell mass is of diagnostic value only in polycythemia where it helps greatly in differentiating polycythemia vera from the symptomatic type. In symptomatic polycythemia the amount per kg. is not significantly increased, even with a marked increase in red cells per c.mm.[1]

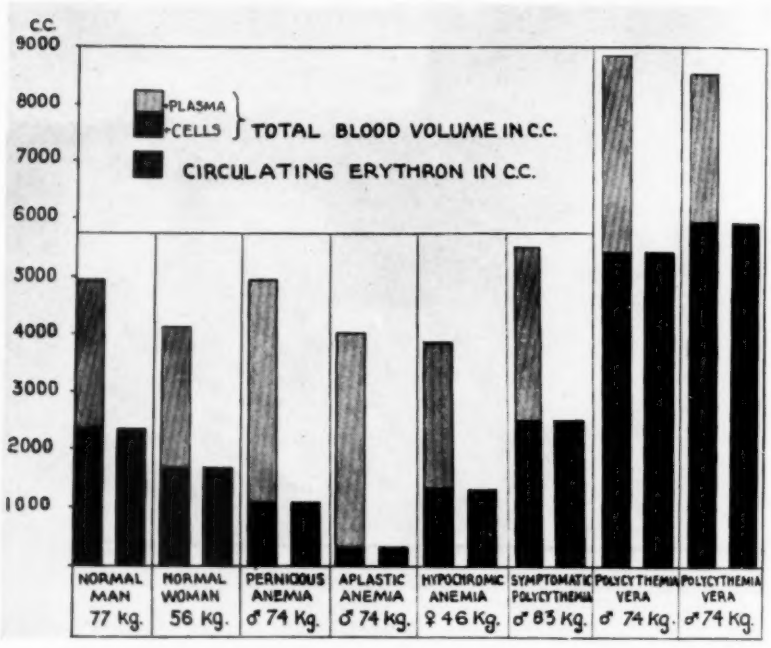
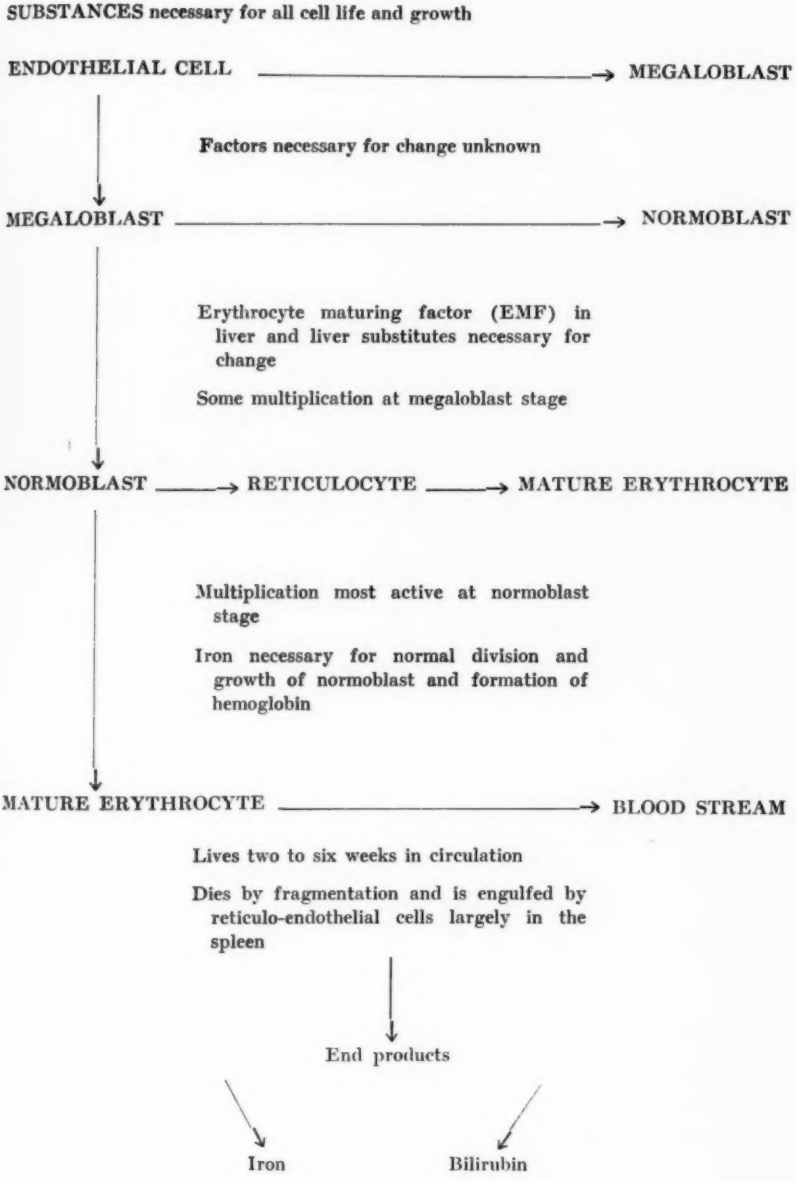


Fig. 3—The circulating erythron as determined from total blood volume and hematocrit readings varies greatly in the blood dyscrasias.

The erythrocyte, the unit of the erythron, is constantly changing. New red cells are formed and old cells are disposed of at a rapid rate. An erythrocyte lives only three to four weeks, so about a trillion cells are destroyed and replaced daily. The stages through which every red cell must pass are summarized in Table I. The bone marrow may be visualized as a grist mill (Fig. 4) into the hoppers of which the materials to make new red cells are constantly being fed.[2] A stream of new erythrocytes is constantly pouring into the circulation to replace the old cells removed by the spleen. To make new cells, two specific substances, iron and the erythrocyte maturing factor (EMF) supplied by liver and liver substitutes, are necessary as well as the basic substances present in all cells. The only recognizable remains of the red cells are bilirubin and iron which are formed as end-products of hemoglobin destruction. Iron, the inorganic element necessary for the formation of hemoglobin, is the only

TABLE I

LIFE HISTORY OF THE ERYTHROCYTE


SUBSTANCES necessary for all cell life and growth
ENDOTHELIAL CELL
MEGALOBLAST
Factors necessary for change unknown
MEGALOBLAST
NORMOBLAST
Erythrocyte maturing factor (EMF) in liver and liver substitutes necessary for change
Some multiplication at megaloblast stage
NORMOBLAST
RETICULOCYTE
MATURE ERYTHROCYTE
Multiplication most active at normoblast stage
Iron necessary for normal division and growth of normoblast and formation of hemoglobin
MATURE ERYTHROCYTE
BLOOD STREAM
Lives two to six weeks in circulation
Dies by fragmentation and is engulfed by reticulo-endothelial cells largely in the spleen
End products
Iron
Bilirubin

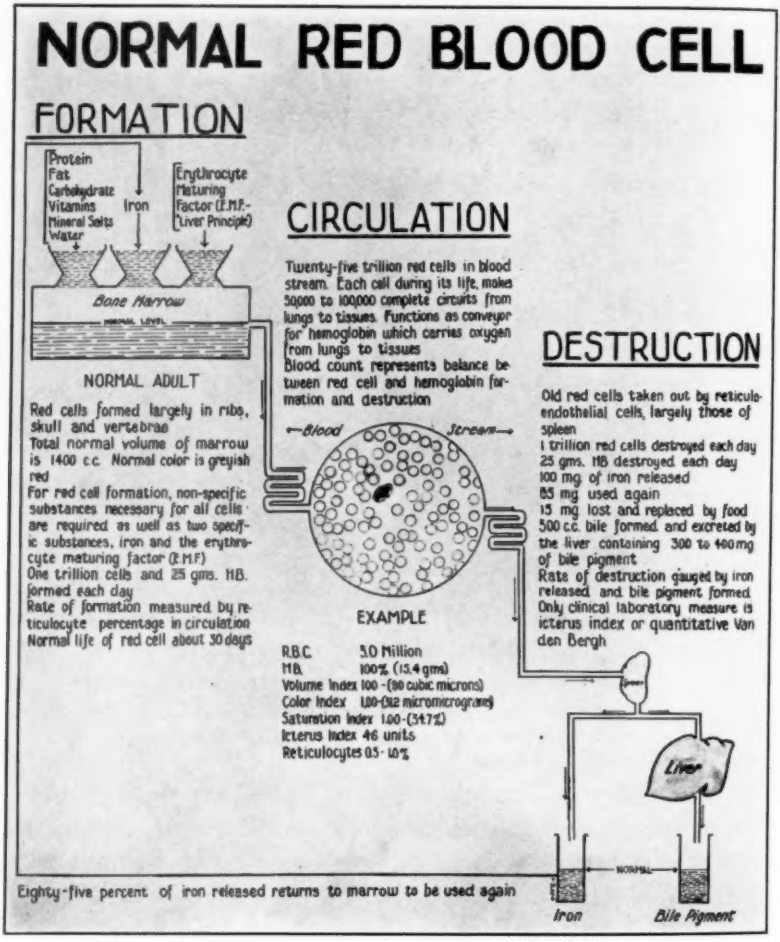

NORMAL RED BLOOD CELL
FORMATION
Protein
Fat
Carbohydrate
Vitamins
Mineral Salts
Water
Iron
Erythrocyte Maturing Factor (E.M.F.-Liver Principle)
Bone Marrow
NORMAL ADULT
Red cells formed largely in ribs, skull and vertebrae
Total normal volume of marrow is 1400 c.c. Normal color is greyish red
For red cell formation, non-specific substances necessary for all cells are required as well as two specific substances, iron and the erythrocyte maturing factor (E.M.F.)
One trillion cells and 25 gms. HB. formed each day
Rate of formation measured by reticulocyte percentage in circulation
Normal life of red cell about 30 days
CIRCULATION
Twenty-five trillion red cells in blood stream. Each cell during its life, make 30,000 to 100,000 complete circuits from lungs to tissues. Functions as conveyor for hemoglobin which carries oxygen from lungs to tissues
Blood count represents balance between red cell and hemoglobin formation and destruction
←Blood Stream→
EXAMPLE
R.B.C. 5.0 Million
HB. 100% (13.4 gms)
Volume Index 100 - (90 cubic microns)
Color Index 1.00-(32 micromicrograms)
Saturation Index 1.00-(34.7%)
Icterus Index 4-6 units
Reticulocytes 0.5 - 1.0%
DESTRUCTION
Old red cells taken out by reticulo-endothelial cells, largely those of spleen
1 trillion red cells destroyed each day
25 gms. HB destroyed each day
100 mg. of iron released
85 mg. used again
15 mg. lost and replaced by food
500 c.c. bile formed and excreted by the liver containing 300 to 400 mg. of bile pigment
Rate of destruction gauged by iron released and bile pigment formed
Only clinical laboratory measure is icterus index or quantitative Van den Bergh
Liver
Eighty-five percent of iron released returns to marrow to be used again
Iron
Bile Pigment

Fig. 4—The physiology of the normal red cell. A cell lives about thirty days so about one trillion cells and 25 grams of hemoglobin are destroyed and formed every day.

constituent known to be used over and over.

Certain laboratory studies are necessary to detect variations in the red cell. These are relatively simple and can be carried out accurately (Fig. 5). The exact total red cell mass is calculated from the total blood volume and the hematocrit reading. The total blood volume is normally so con-

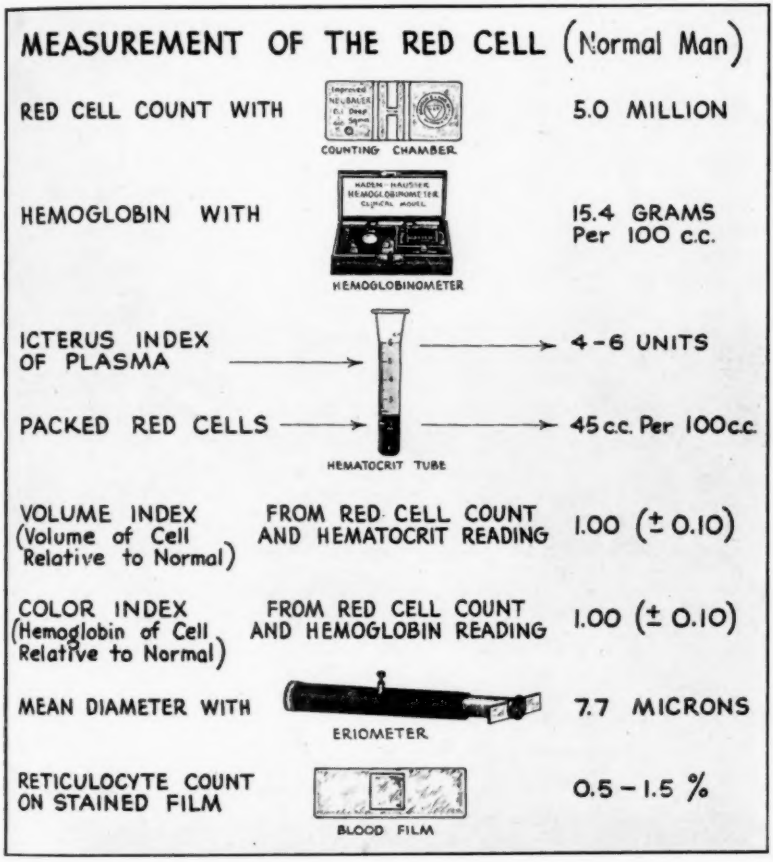


Fig. 5—The measurement of the number, volume, hemoglobin content, and diameter of the red cell is simply done. The icterus index measures the rate of red cell destruction and the reticulocyte count the rate of release of new cells into the circulation.

stant that it seldom needs to be measured except in polycythemia. In all cases the hematocrit reading, the hemoglobin, the red cell count, the bilirubin content of the plasma, and the percentage of reticulocytes are determined. Blood films are studied to detect qualitative changes and for measuring the mean diameter of the erythrocytes. The technique for such a blood study has been discussed fully elsewhere.[3]

The necessary determinations are made as follows:

1. *Red cell count* done in the usual manner.
2. *Hematocrit reading* in cubic centimeters obtained by centrifuging a measured amount of blood mixed with an isotonic coagulant. From the red cell count and hematocrit reading are figured:
   a. The *mean cell volume* in cubic microns.
   b. The *volume index* which records the mean cell volume relative to normal.
3. *Hemoglobin* in grams. From the red cell count and the hemoglobin are calculated:
   a. The *mean cell hemoglobin* content in micromicrograms.
   b. The *color index*, which records the mean cell hemoglobin relative to normal.
4. *Icterus index* as a measure of the bilirubin by comparing the color of the plasma with a standard solution of potassium bichromate.
5. *Reticulocyte count* on a film stained with brilliant cresyl blue.
6. *Mean cell diameter* measured by a diffraction method.
7. *Examination of a stained film* for qualitative changes in cells.

In recording the volume and hemoglobin content of the mean cell, the volume index and color index which express the findings relative to normal are preferred. The mean cell volume and mean cell hemoglobin are absolute figures but indicate nothing except in comparison with the normal. This relation is shown directly by the volume and color indices.

Instead of measuring the mean cell diameter only, a distribution curve (Price-Jones) which records the variation in diameter of cells may be determined by measuring the diameter of a large number (500 or more) of cells (Fig. 6). This procedure is very time-consuming. The volume of the cell is a much more sensitive indicator of a change in size than is the diameter, however, since it records thickness as well as diameter. A 14 per cent increase in diameter corresponds to a 40 per cent increase in volume if the thickness is increased equally with the diameter. In certain instances the diameter may be increased even with a decrease in volume or decreased without a corresponding change in volume. If the anisocytosis is marked, the base of the distribution curve is wide but the type of distribution curve is of no special clinical significance. Since the mean cell volume is so easily determined and is such a sensitive indicator of any change in cell size, we much prefer this to the distribution curve (Price-Jones).

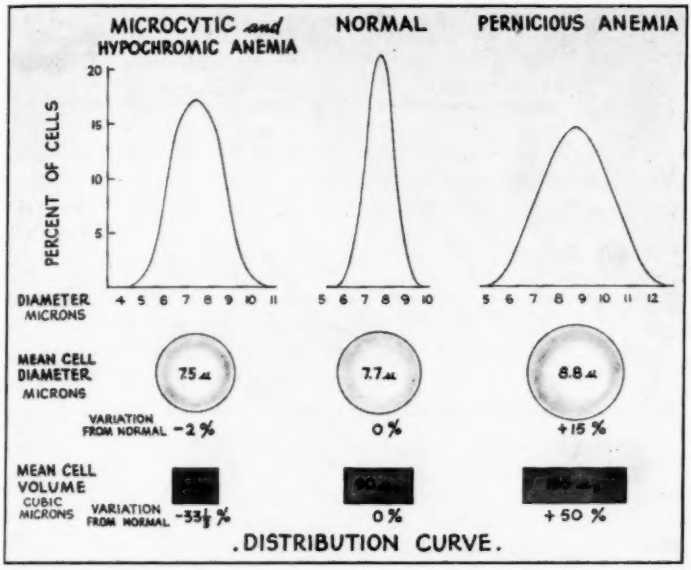


Fig. 6—Distribution curves (Price-Jones) of the red cell. These show the degree and anisocytosis by the spread of the curve as well as the mean diameter. The change in volume is much greater than the change in diameter, however.

The mean cell thickness may be important in relation to the diameter. This is calculated with the aid of a three-dimensional chart from the mean volume and the mean diameter.

After the exact state of the red cell is determined as outlined, what application is to be made of the data? The first and most important use is to classify the anemias. The only satisfactory laboratory classification is based on the size and hemoglobin content of the mean red cell. On this basis there can be only six different types of anemia (Fig. 7). They are:

1. *Normocytic and normochromic.* The mean cell has a normal volume and hemoglobin content. Volume index and color index, 1.00 ($\pm$ 0.10). [Fig. 7, 1]
2. *Normocytic and hypochromic.* The mean cell has the normal volume but is incompletely filled with hemoglobin and so has less than the normal quota. Volume index, 1.00 ($\pm$ 0.10) and color index, $<$ 1.00. [Fig. 7, 2]

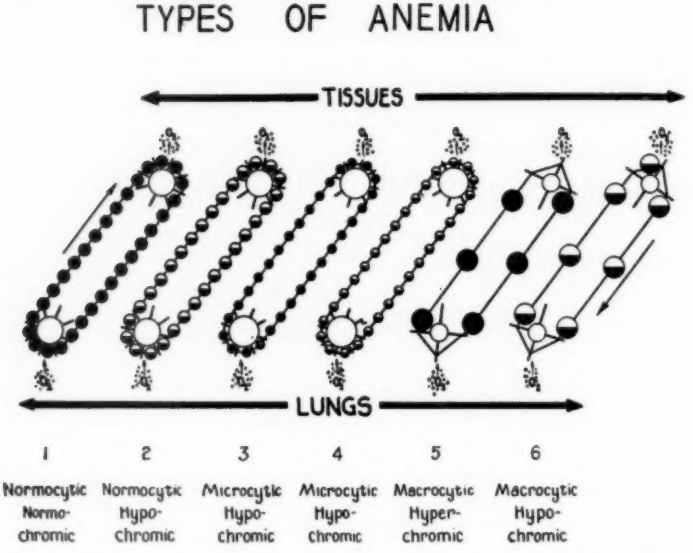


Fig. 7—Types of anemia represented as varying kinds of endless-chain conveyors.

3. *Macrocytic and hyperchromic.* The mean cell has a volume larger than normal and more than the normal amount of hemoglobin. Volume and color index, > 1.00. [Fig. 7, 5]
4. *Macrocytic and normochromic.* The mean cell is larger than normal but contains a normal amount of hemoglobin although the concentration is less than normal. Volume index, > 1.00, and color index 1.00 (± 0.10). [Fig. 7, 6]
5. *Macrocytic and hypochromic.* The mean cell is larger than normal and contains less than the normal quota of hemoglobin. Volume index, > 1.00 and color index, < 1.00. [Fig. 7, 6]
6. *Microcytic and hypochromic.* The mean cell is smaller than normal and contains less than the normal amount of hemoglobin. Volume and color index, < 1.00. [Fig. 7, 3 and 4]

An accurate study of the red cell also affords necessary information concerning the cause of an anemia. An anemia is only a loss of balance between red cell formation and red cell destruction. An erythrocyte

TABLE II

CLINICAL CLASSIFICATION OF ANEMIA

I. Increased blood loss
   A. Mechanical loss from hemorrhage
   B. Accelerated red cell destruction by:
      1. Hemolytic agents (as phenylhydrazine or bacterial toxin)
      2. Rapid red cell removal from an abnormality of cell shape (as congenital hemolytic icterus), overactivity of reticulo-endothelial system, or defect in cell structure

II. Decreased blood formation
   A. Quantitative decrease in red marrow from aplasia as in benzol poisoning, or crowding out of erythrogenic tissue as in leukemia or myeloma
   B. Quantitative depression of marrow activity as by malignancy, hypometabolism, chronic toxemia such as nephritis or cachexia
   C. Qualitative decrease in marrow activity from deficiency of specific substances necessary for normal marrow activity
      1. Deficiency in supply, absorption, or use of erythrocyte maturing factor (EMF) as in pernicious anemia or sprue
      2. Deficiency in supply, absorption, or use of iron as in chronic hemorrhage, dietary lack, and idiopathic hypochromic anemia

count shows nothing but the relation between these two phases of the red cell. In clinical hematology it is necessary to know the rate at which cells are being formed and destroyed and the basis for the loss of balance producing an anemia or polycythemia. A lack of cells and hemoglobin may be due either to an increased destruction or to a decreased formation of cells. The most logical clinical classification of anemia is based on these two fundamental factors, increased red cell loss, and decreased red cell production. A clinical classification of anemia based on this method of production is shown in Table II.

The number of red cells per c.mm. gives no clue concerning the rate of new cell formation or of loss of cells. It does record the balance at the time the count is done. The reticulocyte level shows the number of young cells in the circulation. If there is an excessive number of reticulocytes, new cells are being released from the marrow in abnormally large numbers since the reticulation persists in the cell after reaching the circulation for only a short time. It is apparent that the marrow must be hyperactive if many new cells are being released. On the other hand if the reticulocytes are below normal in an anemia, red cells are not being released from the marrow. This may be due to hypoplasia or to underfunction of the

TABLE III

MEASURES OF RED CELL ACTIVITY

Factor	Indicator
Balance of red cell and hemoglobin formation and destruction	Red cell count and hemoglobin content
Rate of destruction of red cells	Level of bile pigment in plasma
Rate of regeneration of red cells	Level of reticulocytes in circulation
Deficiency of erythrocyte maturing factor (EMF)	Macrocytosis of red cells
Deficiency of iron	Hypochromia and microcytosis of red cells

marrow unless the specific materials necessary for making red cells are deficient. Here the marrow may be hyperplastic and filled with abnormal or incomplete cells. The typical examples of this condition are pernicious anemia due to a lack of erythrocyte maturing factor (EMF) and an iron deficiency anemia. In both instances the marrow is hyperplastic but there is an anemia and a low reticulocyte count because the cells cannot be normally completed and so are not released from the marrow.

In the absence of biliary tract disease which prevents the normal excretion of bilirubin, an excess of bilirubin in the blood can result only from an abnormally rapid breakdown of hemoglobin following a very rapid destruction of red cells. Bilirubin so formed unites with protein and is excreted by the liver and kidneys with difficulty. For this reason an excessive destruction of red cells and hemoglobin is shown quickly by an increased icteric index or bilirubin content of the blood plasma.

Likewise if less than the normal amount of hemoglobin is being destroyed the icteric index falls, often to a low level.

A deficiency in erythrocyte maturing factor (EMF) is detected by a macrocytosis of the red cells and an iron lack by a hypochromia and microcytosis.

The measures of red cell activity are summarized in Table III.

In an anemia produced by an acute mechanical loss of blood the cells remaining are unchanged, so the only findings are the reduction below normal of the number of cells and a corresponding decrease in hemoglobin without alteration in size or hemoglobin content of the mean red cell. If the anemia is due to increased hemolysis of cells there is always an increased production of bile pigment which is quickly retained in the blood plasma and shows as an increased icterus index. Unless the bone marrow is injured by the same process which causes the increased hemolysis, there is a rapid outpouring of young red cells to compensate for the increased loss. These are detected in the circulation as reticulocytes. The reticulocytes are larger than normal as is characteristic of young cells. The typical picture of a hemolytic anemia due to some toxic agent is thus an anemia with increased icterus index, increased reticulocyte count, and slight increase in volume index due to an increase in the volume of the mean cell. The picture in a hemolytic jaundice due to an abnormal shape of the red cell is different and is discussed elsewhere. The anemias due to increased blood loss are illustrated in Fig. 8.

The red cell in an anemia due to depression of marrow activity is usually little changed from normal. The process here is thought of as slow activity of the grist mill but with the production of normal cells. The marrow may be depressed by many general conditions such as a toxemia from nephritis, hypothyroidism, or malignancy. Likewise the amount of functioning marrow tissue may be decreased by leukemia, myeloma, or idiopathic aplasia without materially changing the size or shape of the cell produced.

If an anemia is due to a scarcity of building materials the red cells usually show evidence of such a lack quickly. As the erythrocyte develops in the marrow and maturation takes place, the cell becomes smaller as the specific maturing principle (EMF) furnished by liver or liver substitutes is incorporated in it. When this principle is lacking the cells are always large unless some other factor influencing the size of cells is active. As the specific maturing principle is supplied the cell volume becomes normal. Macrocytosis of the red cell may thus measure the need for the erythrocyte maturing factor (EMF) and also show the completeness with which this lack is supplied. The icterus index is somewhat increased since cells which cannot be completed die in excessive numbers in the marrow.

When iron is missing hemoglobin cannot be formed. With a defi-

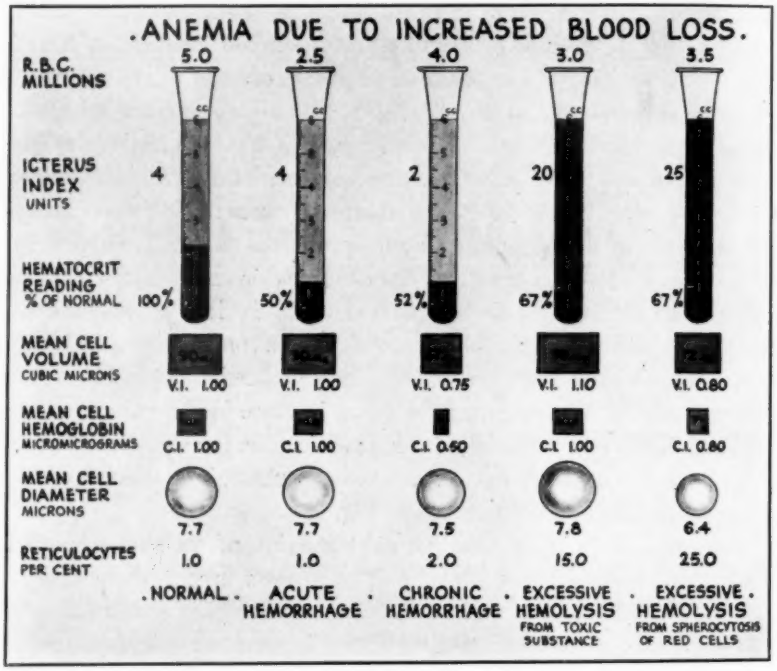


Fig. 8—The anemias due to increased blood loss. If the blood loss is due to chronic hemorrhage, the icterus index is low and the cells are small and deficient in hemoglobin; if due to increased hemolysis, the cells tend to be larger, the reticulocyte count is elevated, and the icterus index is higher.

ciency of hemoglobin there is a hypochromia or low concentration in the cell and if a low hemoglobin content continues the cell decreases in size. This microcytosis seems to be due to the fact that the sole function of the cell stroma is to hold hemoglobin. If hemoglobin is lacking the cell becomes smaller since there is no use in having stroma if there is no hemoglobin to transport. A hypochromia of the red cell as shown by the low color index or a microcytosis as shown by the low volume index thus indicates a deficiency in iron.

The anemias due to decreased red cell formation are shown in Fig. 9.

Rarely both the erythrocyte maturing factor (EMF) and iron are

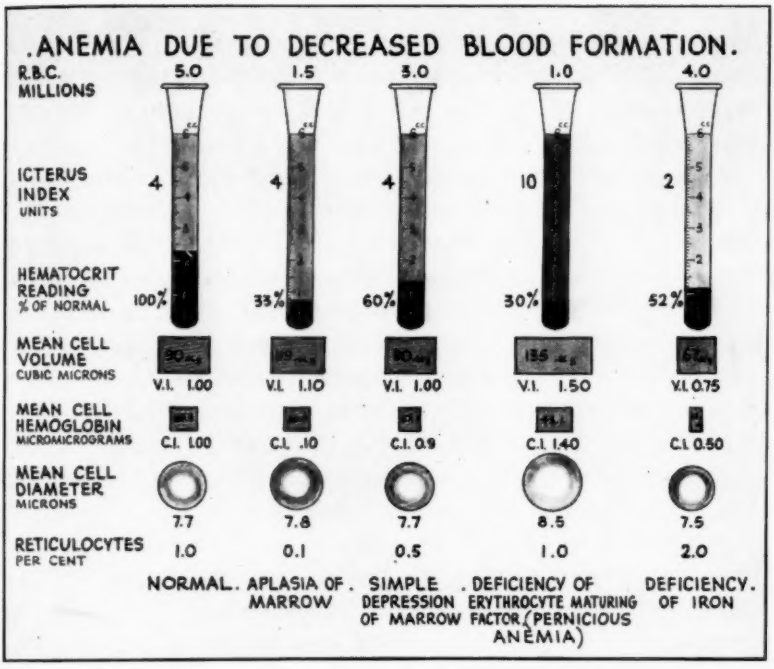


Fig. 9—The anemias due to decreased blood formation. If the decreased blood formation is quantitative, the mean cell varies little from normal; if due to a deficiency in building materials, the mean cell is small with a lack of iron and large with a lack of the erythrocyte maturing factor supplied by the liver.

deficient. Since a lack of the erythrocyte maturing factor (EMF) produces a macrocytosis and a lack of iron, a microcytosis, the algebraic sum of both deficiencies may result in a cell of normal size.

Wherever there is a disordered erythropoiesis, the shape of the cell may be disturbed. Thus in pernicious anemia due to a lack of erythrocyte maturing factor (EMF) or an iron deficiency anemia the cells are not only small or large but may also be abnormal in shape. Such a variation or poikilocytosis has no significance except to indicate a marked disturbance in red cell formation.

The most interesting abnormalities in the shape of red cells are the congenital variations. While the cell is normally a biconcave disk, the

prevailing cell may be globe-, oval-, or sickle-shaped. These shapes represent congenital anatomic malformations similar to a steeple-skull, the absence of iris pigment, or a patent interventricular septum. Such cells function just as efficiently as biconcave disks but are taken out of the circulation more rapidly than new cells can be formed, so, an anemia usually results.

The almost constant anemia of congenital hemolytic icterus is due to the characteristic globe cell or spherocyte. This peculiarly shaped cell is the congenital abnormality of the disease. The shape of the cell may show all variations from the normal biconcave disk to a true sphere. The fragility varies directly with the degree of spherocytosis. A red cell before hemolyzing in a hypotonic salt solution assumes the spheroid form. If the cell tends to be normally spheroid it is apparent that it is already on the way to hemolysis, so hemolysis becomes complete in a much less hypotonic solution of sodium chloride than with cells of normal shape. The spleen seems "tuned" to the normal cell, the biconcave disk. When cells of an abnormal shape come to it, they are quickly filtered out. Normally these are only the disintegrating cells. In sicklocytosis, ovalocytosis, or spherocytosis, the abnormally shaped cells are rapidly removed from the circulation just as old cells are. The length of life of the erythrocyte when the shape is abnormal may thus be only a few days as contrasted with the normal three to four weeks. The anemia of congenital hemolytic icterus thus results from the shape of the cells and not from the increased fragility. The fragility may be correlated directly with the degree of spherocytosis.[4]

Red cells may become larger from conditions other than a deficiency of the erythrocyte maturing factor (EMF) although this is the most common cause. With a marked reticulocytosis, the mean cell is nearly always somewhat increased in volume because reticulocytes as young cells are larger than mature erythrocytes. Likewise in a true aplastic anemia where the red cell formation reverts to a primitive level, the mean volume increases. It is not uncommon to find a macrocytosis in nutritional deficiency disease other than pernicious anemia. Thus in sprue and pellagra the mean cell volume may be increased. Here, however, this finding may be due to a lack of erythrocyte maturing factor (EMF) or some interference with its use.

In cirrhosis or other diseases of the liver, large red cells are frequently present. In cirrhosis there is usually a true macrocytosis as shown by an

increase in volume. The determination of mean red cell volume may be a valuable measure of liver function. It has not been proved whether this macrocytosis is due to a disturbance in storage of the erythrocyte maturing factor (EMF) and so an insufficient supply to the marrow or to the fact that the liver in some way enters into the utilization of the erythrocyte maturing factor (EMF). There is also another characteristic change in red cells in relation to liver disease. With simple obstructive jaundice the red cell almost always increases in diameter without changing in volume. Here the erythrocyte is a much flattened biconcave disk. Such a cell is more resistant to hemolysis than is a normal cell and returns to normal shape when the biliary obstruction is relieved.

Small red cells or microcytosis may result from an exhaustion of the marrow from any cause. Some microcytes are present in almost every type of serious anemia. The most important cause for a microcytosis, however, is a defect in supply or utilization of iron, so, less hemoglobin than normal is present. With the deficient supply of hemoglobin there is no need for stroma to contain it. The total mass of stroma falls usually by decreasing the volume of the mean cell. As a rule the number of cells per c.mm. changes little. With a microcytosis there is almost always a lower concentration of hemoglobin in the red cells as the diminution in mass of stroma seldom equals the decrease in hemoglobin. A hypochromia of the red cells is common even with an adequate supply of iron. Many factors, such as infection, toxemia, or hypometabolism may prevent the proper utilization of iron by the marrow cells and so produce a hypochromia. A hyperchromia in the sense of an increased concentration of hemoglobin per unit volume of cell is impossible since stroma cannot be supersaturated. If the cells are large, more than the normal quota can be carried in each cell due to the increase in volume of stroma.

Accurate data on the red cell also helps greatly in treating the anemias. A macrocytosis usually indicates a deficiency of the erythrocyte maturing factor supplied by liver. In treating pernicious anemia the primary indication is to supply the missing factor continuously in adequate amount. When adequately supplied, the macrocytosis of the red cells disappears as shown by the return of the volume index to normal. If a macrocytosis persists, the treatment is incomplete. When liver therapy is first instituted in an active untreated case of pernicious anemia, there is a tremendous outpouring of reticulocytes or young cells which are completed by supplying the erythrocyte maturing factor. These are

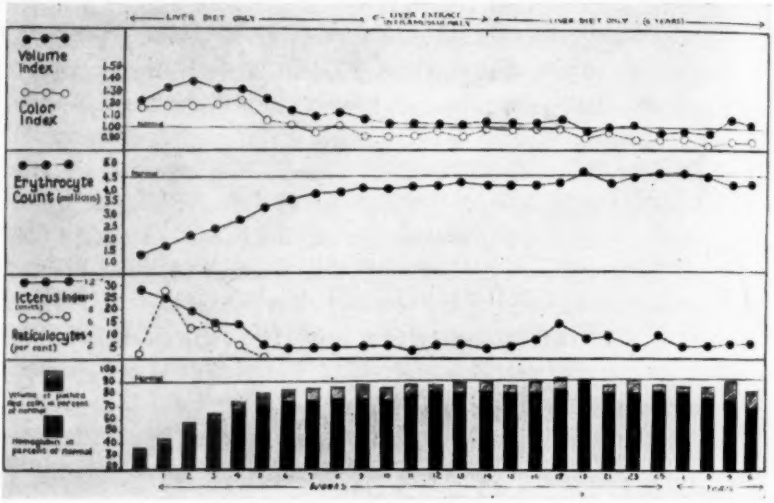


Fig. 10—The red blood cell in pernicious anemia with adequate liver therapy. The volume index is high before treatment and returns to normal. So long as the treatment is adequate the volume index remains normal.

usually larger than normal so the volume index may rise for a time with the reticulocytosis. The icterus index quickly falls showing that the cells are no longer dying abnormally in the marrow because they cannot be completed. Soon the red cell count, the hemoglobin, and the volume index return to normal (Fig. 10). The purpose of treatment is to have them remain so. Long before any clinical symptoms arise as a result of the disease, deficiency in the needed factor may be detected by a rise in the volume index.

The course of an iron deficiency anemia may also be followed by determining the volume index and color index. The characteristic low volume index and color index rise to normal if iron is adequately supplied and is used by the marrow (Fig. 11).

Other qualitative changes in erythrocytes such as basophilia and nucleation have little significance. These only indicate the marrow activity of which the most sensitive indicator is the number of reticulocytes.

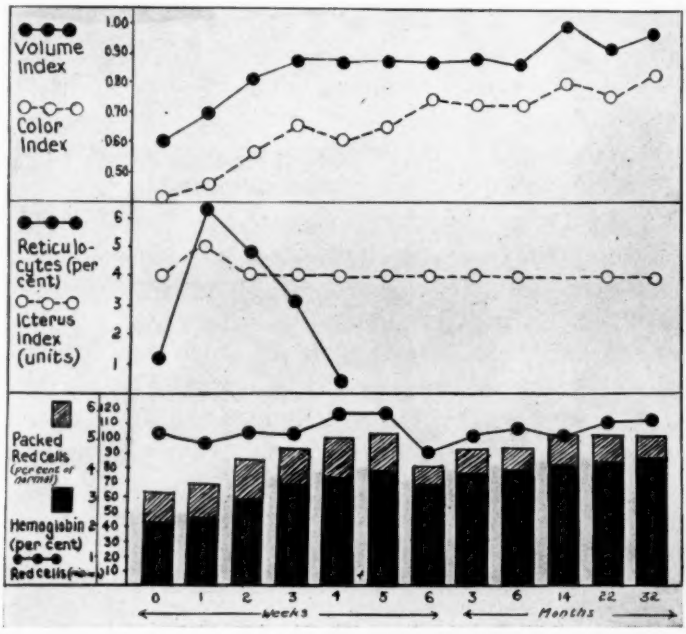


Fig. 11—The red blood cell in an iron deficiency anemia. Here the mean cell is small as indicated by a low volume index and is deficient in hemoglobin (low color index). With adequate iron therapy, the volume and color indices gradually rise while the red cell count changes little.

Summary

In every blood dyscrasia an accurate study of the red cell is necessary. This study should routinely include:

1. Red cell count
2. Hemoglobin estimation
3. Hematocrit reading
4. Mean cell diameter
5. Volume index as measure of mean cell volume
6. Color index as a measure of mean cell hemoglobin content
7. Stained film for reticulocyte count, basophilia, nucleation and abnormalities in shape
8. Icterus index

Exceptionally we need also:

1. Total blood volume
2. Total red cell mass
3. Distribution curve (Price-Jones) of cell diameter
4. Calculation of thickness

An increase in red cell mass per kilogram of body weight occurs only in polycythemia vera; a decrease occurs in all anemias.

The red cell count and hemoglobin show only the balance between blood formation and destruction at the moment the test is made.

The icterus index measures the rate of hemoglobin destruction and thus indirectly of red cell loss.

The reticulocyte count measures the rate of release of red cells from the marrow, and thus indirectly records the activity of the marrow.

A deficiency of erythrocyte maturing factor (EMF) is shown by a macrocytosis; a deficiency of iron is shown by a hypochromia or microcytosis.

The volume and hemoblogin content are the best indicators of (1) the lack of the specific maturing factor supplied by liver and by iron, and (2) the adequacy of supply of these factors in an anemia due to such a deficiency.

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POLYCYTHEMIA*

PAUL REZNIKOFF

INTRODUCTION AND CLASSIFICATION

POLYCYTHEMIA means an increase in red blood cells per unit volume of blood above a value which is considered normal. There are many causes for this state but whether the exact etiology is apparent in any given case or not, it is clear that the more knowledge we have about polycythemia, the more probable it is that all polycythemic states are either secondary or overcompensatory mechanisms to some general or local physiological or pathological change, rather than primary conditions.

While many classifications of polycythemia exist, probably the simplest is the division into two groups, suggested by Harrop and Wintrobe[1]—a mild type which might be called erythrocytosis, similar to leukocytosis; and the pronounced state or erythremia, analogous to leukemia. From a physiological viewpoint polycythemia may be (a) relative, as seen in conditions in which there is a loss of plasma; (b) transient, such as occurs after splenic contraction; and (c) absolute, when the total cell mass as well as the total blood volume shows a sustained and pronounced increase.

Erythrocytosis need concern us little in this discussion. It is seen in a variety of conditions and circumstances, such as congenital heart disease, mitral stenosis, pulmonary arteriosclerosis; at high altitudes; secondary to the action of many chemicals; and after hemorrhage.

Erythremia,[2] however, presents a distinct clinical picture and has been known by various names, as polycythemia vera, or polycythemia rubra. It is instructive in reviewing a disease to go back to original papers and see how much progress has really been made since a pathological concept was first described. In 1892 Vaquez[3] definitely claimed that polycythemia was due to hyperactivity of the hematopoietic organs, and

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in 1903 Osler[4] established all the cardinal evidences of this condition—cyanosis, polycythemia, and splenomegaly. It is also interesting to note that of his own four patients, one was a Russian Jew and one a Turkish Jew. In his 1908 paper[5] he suggested that anoxemia was the important pathological mechanism responsible for polyglobulism and mentioned the possibilities of x-ray therapy. These ideas are probably the most important features of polycythemia as we know it today.

Etiology

Many causes have been proposed to explain the etiology of erythremia. That a familial or hereditary type exists is generally accepted. The reports of Engelking[6] and of Spodaro and Forkner[7] give two excellent descriptions of this form. An outstanding feature of the familial, as contrasted with the ordinary type, is the fact that the individuals who have hereditary polycythemia rarely suffer from the severe symptoms of the disease. While an endocrine factor has been suggested because of the erythrocytosis in cases of pituitary basophilism,[8] hyperthyroidism, and suprarenal tumors, in most of these latter conditions the increase in erythrocytes rarely reaches the degree found in the ordinary type of polycythemia. Occasionally splenic tuberculosis and thrombosis of the splenic vein may also be characterized by an elevated red cell count, but these conditions are rare. A neoplastic conception of the cause of polycythemia is not generally accepted because of the absence of abnormal cells and the lack of invasiveness. A few reports[9,10,11] have been published of cerebral lesions inducing erythremia, such as injury to the proximal part of the vegetative brain centers, or diseases like encephalitis. Morris'[12] conception that polycythemia is due to excess secretion of a gastric substance, addisin, has not been verified by most workers.

This disease is most prevalent in males in middle or late life and there seems to be a preponderance among Jews born in Eastern Europe. This can be illustrated by a study of six institutions[13] in which the incidence of erythremia in this group was about 48 per cent contrasted with less than 10 per cent of general admissions. Such a finding naturally suggested an analogy to thromboangiitis obliterans and induced us to investigate the blood vessels of the bone marrow. It is important to make such studies on the bone marrow of subjects whose blood counts have approached normal by therapy to avoid excessive congestion of the bone marrow vessels which tends to make the vasculature scarce and, even in normal tissue,

Fig. 1—Artery in bone marrow of normal subject. Magnified × 280. Practically no fibrous tissue infiltration of wall of vessel.

Fig. 2—Artery in periosteum of arteriosclerotic patient. Magnified × 280. Fibrous tissue infiltrating muscularis.

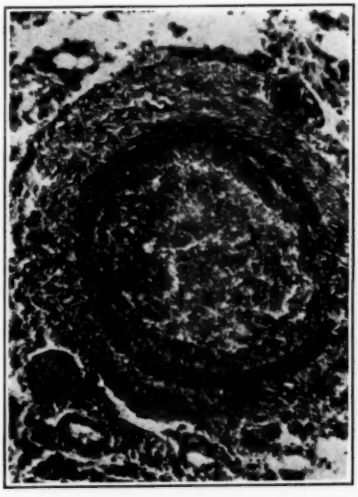

Fig. 3—Artery in bone marrow of a polycythemic patient. Magnified × 110. Marked fibrosis of subintima and adventitia.

TABLE I

RACIAL AND NATIONAL ORIGIN OF PATIENTS SUFFERING FROM POLYCYTHEMIA VERA

Institutions	*Total No. of patients (polycythemia vera)*	*Patients of Jewish origin born in eastern Europe (polycythemia vera)*		*General admission of patients of Jewish origin born in eastern Europe*
		No.	*Per cent*	*Per cent*
Bellevue Hospital	28	14	50	3 (sample year)
Cornell Clinic	7	4	57	12 (estimate)
New York Hospital...	19	12	63	9 (sample year)
Presbyterian Hospital.	33	13	39	15 (race not given; eastern European birth)
St. Luke's Hospital...	34	15	44	7 (race not given; eastern European birth)
New Haven Hospital..	13	6	46	10 (estimate)
	134	64	47.8	9 (approximate)

difficult to visualize. It is also essential to use a Masson trichrome stain to bring out the fibrous tissue adequately. Under such conditions it was found that in polycythemia the capillaries are markedly thickened and that in most cases the arteries and arterioles show adventitial and subintimal fibrosis. What causes such lesions is not known but it is of interest that in one early case the bone marrow showed inflammatory lesions along the course of the vessels. These observations have led us to propose the theory that erythremia may be due to local anoxemia in the bone marrow itself, with overcompensation of erythrogenesis. Since the lesion is local, the failure to lower the blood count by subjecting a patient to oxygen therapy is easily understood. Whatever the cause of polycythemia, all workers are agreed that the increase of erythrocytes in this condition is not due to decreased destruction or prolonged longevity of the red blood cells but is primarily dependent upon a heightened production.

PATHOLOGY

At autopsy the vessels are found to be engorged; hemorrhages and thromboses are common; the spleen and liver are large and hyperemic; and sometimes cirrhosis is seen. The marrow of the long bones is engorged and that of the short bones frequently is characterized by erythroblastosis and leukoblastosis. Increase of megakaryocytes is usual.

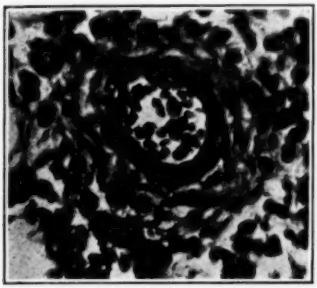

Fig. 4—Arteriole in bone marrow of normal subject. Magnified × 270. No fibrosis in wall of vessel.

Fig. 5—Arteriole in bone marrow of polycythemic patient. Magnified × 540. Fibrous tissue infiltrating entire wall of vessel.

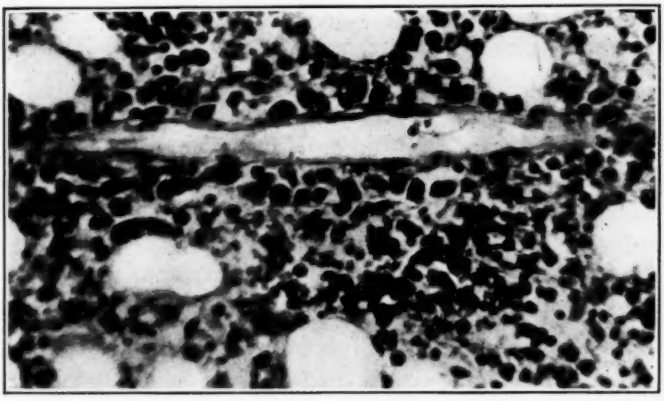

Fig. 6—Capillary in bone marrow of normal subject. Magnified × 270. Thin wall, nuclei bellying into lumen.

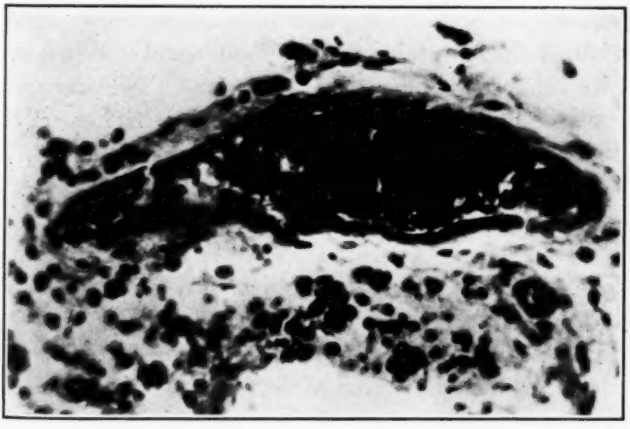

Fig. 7—Capillary in bone marrow of polycythemic patient. Magnified × 290. Marked thickening of wall. Cross section of markedly thickened small capillary in field.

Symptoms and Signs

The symptoms and signs of polycythemia are too well-known to require detailed description. The skin and mucous membranes show a cyanosis which is reddish blue, with dilated superficial vessels. Bleeding is not uncommon from the nose and gums, and these patients usually have bloodshot eyes. Erythromelalgia and skin eruptions occur occasionally. Clubbed fingers are usually absent in true polycythemia, but are seen in the familial type and in erythrocytosis secondary to heart and lung lesions.

Cardiovascular changes are common, especially arteriosclerosis, thrombosis, varicosities, and phlebitis. While true cardiac hypertrophy is rare, the x-ray picture usually shows some increase in heart size. Cardiac decompensation is a late phenomenon. Except for the Gaisböck type of polycythemia, which is really a nephrosclerosis, the blood pressure is only slightly elevated if at all.

Many of the symptoms of polycythemia are related to the nervous system. Usually patients complain of headache, dizziness, and a sense of fullness of the head. Paresthesias and pruritis are common. Vascular accidents in the fundi may cause blindness and the engorged tortuous vessels of the deeply colored retina explain the frequency of visual disturbances. Many complications involving the nervous system are due to the slowing of circulation of the cerebral vessels causing anoxemia.[14] While these occurrences may be transitory, actual thromboses and hemorrhages of the cerebral vessels may produce serious accidents. The average polycythemic patient is depressed and has a sluggish mentality. However, these individuals frequently demonstrate a combination of mental activity and irritability which makes them exceedingly uncomfortable household companions. It must be remembered that even when therapy has brought the blood count to normal, these nervous phenomena may persist and suggest that some of the disturbances are really due to vascular changes rather than to a polycythemia itself.

Many patients complain of pain and fullness in the left upper quadrant due to splenic enlargement, and constipation and flatulence are common. Gastrointestinal hemorrhages and thromboses produce a serious complication in erythremia. Cirrhosis of the liver may occur in the course of polycythemia and this lesion is explained on the basis of long continued congestion. One of the most interesting problems involving the gastrointestinal tract is the relationship of erythrocytosis to duodenal ulcer.[15]

Many of these patients do not have hyperacidity and although thrombosis of the vessels or erosion of distended vessels have been considered as causative factors, many workers now believe that the increase of erythrocytes, which is usually moderate, in many cases of duodenal ulcer is due to bone marrow overcompensation for low grade bleeding.

About three-fourths of all polycythemic patients have splenomegaly. This is not present in the Gaisböck type. The engorgement of the spleen may lead to infarcts and perisplenitis and cause severe pain.

Hirsch[16] has found nodules by x-ray examination of the lungs which he thinks may be subpleural thrombi or small hemorrhages. These disappear in about three weeks.

Laboratory Findings

The hematopoietic system has received much attention in this disease. The average red blood cell count in untreated patients varies between 8 and 12 million per c.mm., and the hemoglobin, which is normal in function, ranges between 18 and 24 gm. per 100 cc. of blood. The cells are usually normocytic, occasionally microcytic. Reticulocytes average between 1 and 2 per cent. Polychromatophilia, basophilic stippling, and even nucleated red blood cells may be found but the factor of hemorrhage or treatment by hemolytic agents must be considered when these immature forms are prevalent. Leukocytosis, polynucleosis, increase in immature polymorphonuclear cells, and thrombocytosis are usual. Tendency to hemorrhage is supposed to be due in part to poor clot retraction because of increase in cellular mass and decrease in serum. It is important, therefore, to undertake surgical procedures, such as dental extractions, with great care and to insist upon the hospitalization of the patient. The viscosity of the blood may be five to eight times normal and the specific gravity varies between 1.075 and 1.080, compared to the normal of 1.055 to 1.065. The sedimentation rate is greatly retarded. Haden[17] has recently emphasized the importance of determining the total red blood cell mass in diagnosing polycythemia. This is greatly increased since the total blood volume may be in some cases almost twice the normal; the hematocrit is markedly increased; and therefore the total cell mass may approach a three-fold rise.

Certain features concerning the hematological complications of polycythemia merit consideration. The relationship of this disease to leukemia has often been described and in fact some believe that there is a definite

disease entity known as erythroleukemia in which both diseases coexist. Others think that erythremia may terminate as a definite leukemia and still another group does not accept these concepts but holds that early in leukemia there may be an irritation of the contiguous erythrogenous bone marrow, giving an increase in red blood cell count. Whatever the true explanation of so-called erythroleukemia may be, it is not difficult to conceive of the contiguous irritation theory as one compatible with our knowledge of the bone marrow. Certainly the leukogenic and thrombocytogenic tissue shows evidence of stimulation in most cases of polycythemia, and this should afford no more surprise than does leukocytosis and thrombocytosis following acute hemorrhage.

Some polycythemic patients finally develop anemia and others thrombocytopenia with purpura. An exhaustion hypothesis has been proposed to explain these phenomena and this also fits in with the theory of the end result of prolonged anoxemia. However, it is important in such complications to be sure that one is not dealing with the final picture of prolonged depression therapy, either x-ray or chemical.

A few miscellaneous observations may be itemized. The basal metabolic rate may be increased. Whether this is due to increased formation of red blood cells or an increase in uric acid is not known. However, it is interesting to note that gout has frequently been reported complicating polycythemia.[18] The blood flow is slow, the skin capillaries distended, the respiratory minute volume is increased, and the vital capacity reduced. Albuminuria is usually present.

Therapy

It is not possible to review in detail all the methods which have been used to treat polycythemia. Therefore, this paper will deal principally with the four types of therapy used most commonly: venesection, acetylphenylhydrazine, irradiation, and Fowler's solution.

Venesection, removing 500 cc. of blood as often as twice a week, has in its favor the rapid amelioration of symptoms such as dizziness and headache. Recent work has shown that such a procedure produces very little bone marrow stimulation.[19]

Acetylphenylhydrazine, in doses of 0.1 gm. daily or every other day, until the blood count begins to fall and thereafter a maintenance dose, is well tolerated by most patients. This drug is not only hemolytic but apparently has some depressing action on the bone marrow. In using

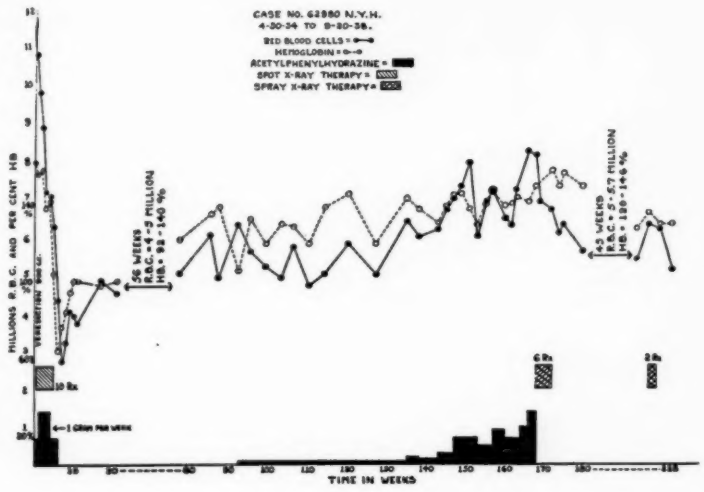

Fig. 8

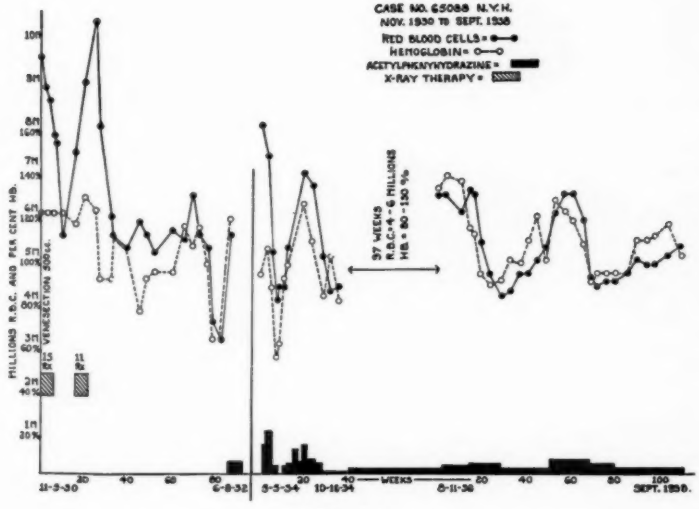

Fig. 9

Figs. 8, 9—Course of polycythemia treated with venesection, acetylphenylhydrazine and irradiation.

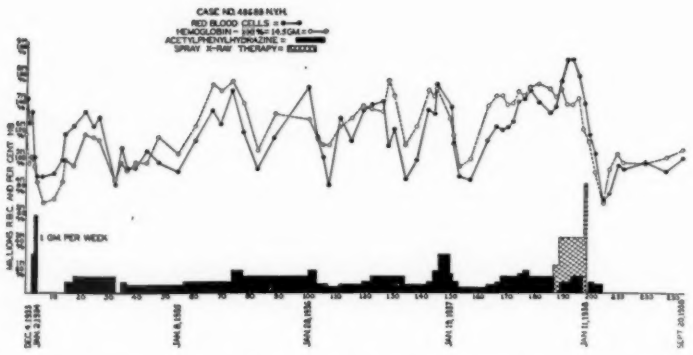

Fig. 10—Course of polycythemia treated with venesection, acetylphenylhydrazine and irradiation.

acetylphenylhydrazine it must be remembered that its action is cumulative and that patients vary markedly in their response to different doses. The incidence of thrombosis during the course of acetylphenylhydrazine therapy is probably no greater than can be explained by the disease itself.

Irradiation of the marrow and of the spleen has been used with success but recently many workers have claimed excellent results with spray radiation.[20] Figs. 8, 9, and 10 illustrate three cases in which these procedures were used.

Fowler's solution, prescribed according to Forkner's method,[21] is an effective drug in polycythemia and its successful use requires careful attention to detail.

Recently, normal propyl disulphide[22] has been suggested as a remedy in erythremia. It apparently has a phenylhydrazine-like action but has the disadvantage of giving the patient an onion odor.

The effectiveness of gastric lavage has not been substantiated nor is it practical.

Polycythemic patients, if properly treated, may have a long life, if not a merry one. It is important for the physician to pay attention to the emotional factors which may cause much unhappiness to the patient. As a general rule it is wise to avoid putting polycythemic patients to bed, since some activity is desirable in a disease complicated by thrombosis.

The diet should exclude condiments, too much roughage, alcohol, and foods and liquids which are very hot, as all of these may irritate the already congested gastrointestinal mucosa. Above all, it is important to keep the patient's blood count at a level which gives the greatest comfort and least complaint, rather than reach some arbitrary base line on a chart. The physician must not treat a blood count but the entire patient.

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CHRONIC GASTRITIS*

RUDOLF SCHINDLER

IN THIS paper I shall confine myself strictly to the discussion of primary chronic nonspecific gastritis. After death the gastric mucosa disintegrates so rapidly that usually postmortem changes can only be recognized by gross and microscopic inspection. Therefore, the diagnosis of chronic gastritis was thoroughly discredited. Only when it became possible to observe the living gastric mucosa through the gastroscope was the frequency and importance of this disease rediscovered and described. Even so, the anatomic foundation of chronic gastritis is uncertain. We do not know very well the histology of the normal stomach of the adult. Material obtained at gastric resection does not give indisputable evidence of the preoperative condition of the stomach, as will be shown later. The normal gastric mucosa of the newborn is better known; it differs from that of adults, and there has been the tendency to make the microscopic diagnosis of chronic gastritis in every adult because of this fact. This is not permissible. There certainly are findings which are the remnants of the frequent acute gastritides of childhood; there is the physiological response of the gastric mucosa to the daily irritation by coarse, hot or cold food. These are the physiological changes the gastric mucosa undergoes. If we should call them pathological, then no adult would have a normal gastric mucosa, and such a definition cannot be accepted.

However, changes are sometimes found which evidently are proof of a disease. In the more severe cases we cannot doubt that a serious gastric disease is present. There is atrophy; the glands have disappeared; there is infiltration, and the epithelium has undergone a metaplasia into intestinal epithelial type; many goblet cells are seen. Such pronounced changes, however, are rarely seen histologically. The pathologist is usually unable to decide whether a gastritis exists or not.

The gastroscopic picture of gastritis is more easily recognized, as I shall endeavor to show you. Gastroscopic examination can be easily carried out repeatedly in healthy and in sick people. If the proper tech-

* Delivered January 5, 1939 at the Annual Meeting of The New York Academy of Medicine.
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nique is used, the patient does not experience any considerable discomfort and, therefore, we are able to examine many patients once a week up to thirty, or even sixty-five, times. Thus we can study normal and diseased stomachs at repeated examinations. The picture obtained by our modern, flexible, safe gastroscope is brilliant and sharp. It permits the visualization of much finer detail than even the inspection of the gross specimen. It is always amazing to see how difficult it is to find a small ulceration in the gross specimen, a lesion seen so readily at gastroscopy. This difference is due to the blood circulating at gastroscopy, absent in the gross specimen.

My conclusions regarding the gastroscopic appearance of the normal stomach were based on a study of healthy people of all age groups.[1] The gastric mucosa of the healthy adult looks smooth, and at the ridge of the folds, glistening, silk-like; it contains high-lights; its color is a uniform orange-red. It should be emphasized that older people also, up to sixty or sixty-five years of age, show the same picture, and we should dismiss the idea that at this age atrophic processes are frequent.

If we examine gastroscopically patients suffering from abdominal distress we often find pictures which differ from those found in healthy people. In almost 50 per cent of these patients we find diffuse alterations. The mucosa may show red patches and layers of adherent, glary, grayish mucus. Such red patches have been described by Beaumont in his famous observations made at the gastric fistula of his servant, Alexis St. Martin, and it is interesting to note that all the changes observed so beautifully by Beaumont and disregarded so entirely for a hundred years, now are rediscovered at the gastroscopic examination. Sometimes the secretion may even be purulent. Histologic checks are rare. However, I obtained the unique microscopic picture of a very outspoken superficial gastritis observed gastroscopically. At a laparatomy a biopsy was taken without the use of any clamps; microscopic sections revealed tremendous superficial infiltration by plasma cells.

If we watch the course of this type of gastritis, which I have called "chronic superficial gastritis," over a period of months or years, two different types of the course are observed. Either the changes disappear, the patient becoming entirely healthy; or chronic atrophic gastritis develops. In some areas of the stomach the signs of superficial gastritis are still seen; in adjacent portions, however, the mucosa becomes thin, mottled, grayish or greenish-gray in color. Atrophy may be patchy, or

Fig. 1 a

Fig. 1, a and b

Gastroscopic (a) and microscopic (b) picture of the normal gastric mucosa. Gastroscopically the normal mucosa is smooth, silk-like. View of antrum, angulus and pylorus.—The microscopic section demonstrates the mucosa of the body of the stomach. Only few interstitial cells are seen.

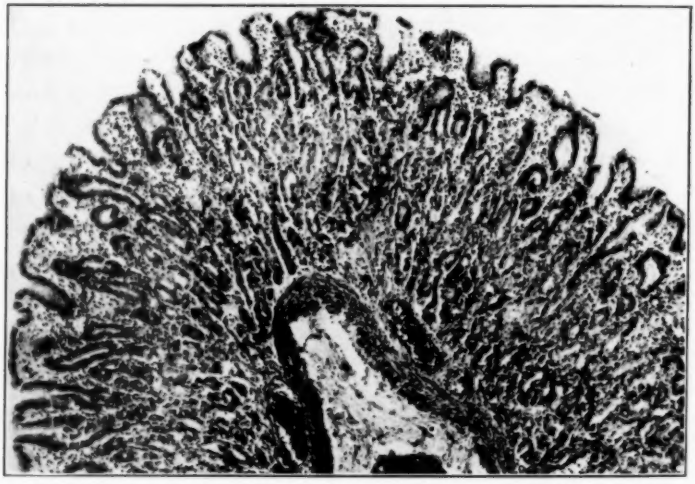

Fig. 1 b

more diffuse, or complete. Blood vessels, always absent in the normal mucosa, are seen. Here the question comes up whether such a condition may still be called inflammation, or do we have to deal with a merely degenerative process. However, this atrophy so often develops from an inflammation. We do not know if there are cases at all without preceding inflammation, nor do we know whether the inflammatory process is entirely gone. In cases of deficiency states, as in pernicious anemia, the first thing we can see gastroscopically is superficial gastritis. Brown has

seen definite inflammatory changes histologically in pernicious anemia; Jones and Benedict[2] observed hypertrophic changes in this disease gastroscopically. For these reasons it seems correct, in the light of our present knowledge, to call this disease an inflammation. Atrophic gastritis may develop within a few months, but then it remains stationary. Jones and Benedict were the first to show that in pernicious anemia following liver therapy, the atrophic gastric mucosa may regain its normal appearance. This observation has been corroborated since, and thus we know that atrophic gastritis is not unchangeable.

There is still a third gastroscopic picture of diffuse inflammation of the stomach which we call hypertrophic gastritis. The gastric mucosa looks swollen, velvety, dull; the high-lights are reduced; nodules and *verrucae* are seen. The folds sometimes look segmented, like a caterpillar. Mucosal hemorrhages are often present. If we have the occasion to examine such a mucosa microscopically, we find proliferation of the surface epithelium and of the glandular apparatus, with tremendous infiltration and enlargement of the lymph follicles. The proliferation may become fan-like or finger-like. Not infrequently superficial ulcerations are observed. These superficial inflammatory ulcerations never develop into true chronic gastric ulcer. The site of predilection of the gastritic changes is the body of the stomach; however, antrum gastritis occurs also, although ulcerative antrum gastritis is very rare.

What are the clinical aspects of chronic gastritis? How frequent is this disease? What is its etiology, its symptomatology, its diagnosis, its therapy? What is its relation to other diseases? European workers have called chronic gastritis one of the "central problems" of internal medicine, and from the observation of over 1,500 cases, I am inclined to agree.

In a statistical survey of gastric diseases as observed gastroscopically in 1,000 patients in the United States and in 255 patients in Germany, we found the incidence of chronic gastritis to be 41.8 and 45.0 per cent respectively.[3] For the clinical analysis all cases combined with some other disease had to be discarded. Even so, much care is needed to avoid faulty conclusions. I will try to summarize briefly the results of our analytical efforts.

The etiology of chronic non-specific gastritis is practically unknown. Most is speculation. Very few facts are proved. It seems to be certain that acute gastritis may develop into chronic superficial gastritis and finally into chronic atrophic gastritis. Chronic superficial gastritis is

Fig. 2a

Fig. 2, a and b

Gastroscopic (a) and microscopic (b) picture of chronic superficial gastritis. Gastroscopically red patches and layers of purulent secretion are seen. Microscopically there is tremendous infiltration with plasma cells only in the upper layers of the mucosa between the crypts and the necks of the gastric glands; one small erosion is seen.

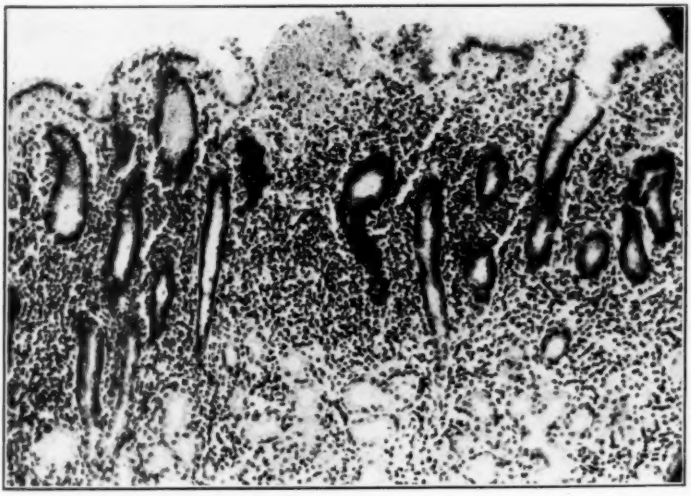

Fig. 2b

frequently found together with infection of the sinuses and of the tonsils, or with chronic infectious diseases such as tuberculosis of the lungs. Alcohol does not play any role in my experience. However, it seems that the habitual use of hard liquor may lead to hypertrophic gastritis. All observers agree that nicotine may play an important role. Gastric retention, as found in pyloric obstruction, may lead to chronic gastritis. The continuous reflux of intestinal juice, as found sometimes in stomachs after operation, may produce a very severe form of gastritis. Since this

is a secondary form, it must be omitted from this discussion. Superficial and later atrophic gastritis may be found as a result of high voltage x-ray therapy of the stomach. That atrophic gastritis occurs in various deficiency states, as in pernicious anemia, is well known. With these few statements our positive knowledge of the etiology is almost exhausted. It seems that bacteriological factors play a minor role as compared with mechanical and chemical factors.

When we analyze the symptoms of an anatomical disease, we hope to find complaints so characteristic as to permit immediate diagnosis.[4] Attempts made by all gastroscopists in this direction have been so far without result. Neither case history nor physical examination, nor laboratory, nor Roentgen findings permit the diagnosis, although a few symptoms, especially in atrophic gastritis, are suggestive. In superficial gastritis the patients complain of epigastric pain, either of the delayed type or coming immediately after meals. Indefinite pressure, heavy feeling, fullness, belching, disagreeable taste in the mouth, nausea and vomiting are often present. At the physical examination sometimes, though unfortunately rarely, a sign is found which, in my opinion, is entirely characteristic. However, my description,[5] published in 1926, has never been confirmed. There is sometimes a tender zone to the left of the navel, which when checked fluoroscopically corresponds exactly with the silhouette of the stomach, and therefore cannot be mistaken for left-sided Head zones of the pancreas or the left kidney, and certainly not for a tender colon. The roentgenologic statement of a tenderness of the gastric silhouette is the only contribution x-ray can make in this diagnosis. Statement of the thickness of the folds, as seen in the x-ray relief pictures, is not diagnostic. Laboratory findings in superficial gastritis are inconclusive. Histamine proved anacidity may be found as well as hyperacidity. Occult blood may be found sometimes in the stools. Sometimes the aldehyde reaction in the urine is strongly positive, indicating participation of the liver.

If the superficial inflammation leads to atrophy the clinical picture changes. The gastric symptoms become less marked, general symptoms being in the foreground of the clinical picture, so that these patients are always treated as psychoneurotics. Weakness and nervousness come in spells. The reason for this is unknown. Two physicians, both suffering from a severe gastric atrophy, told me that during such an attack, which may last several months, they are incapacitated. When Dr. Murphy of

Fig. 3a

Fig. 3, a and b

Gastroscopic (a) and microscopic (b) picture of chronic atrophic gastritis. Gastroscopically the mucosa is thinned so that the net of the submucosal blood vessels becomes visible. Microscopically the mucosa is thin, the glands have disappeared, the epithelial type has changed, many goblet cells are present.

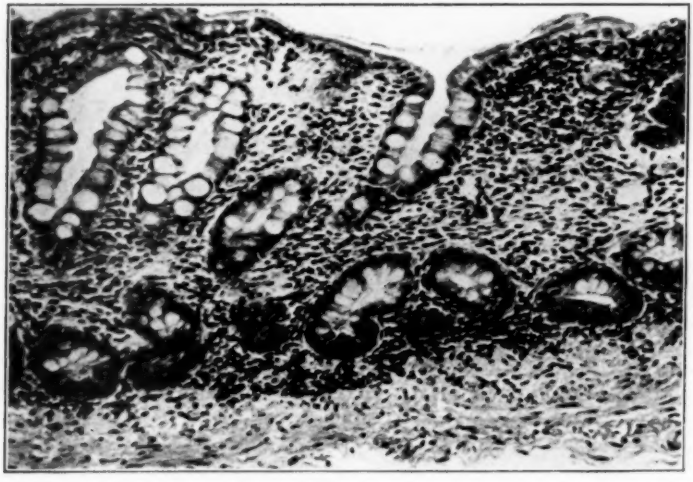

Fig. 3b

Buffalo analyzed with me the records of forty-two patients suffering from uncomplicated atrophic gastritis, the question came up whether or not these general symptoms would be found also in other abdominal diseases. A subsequent analysis of a great number of cases of hypertrophic gastritis, ulcer, cholecystopathy, and similar conditions showed that only in pernicious anemia similar symptoms were found; so that the syndrome of epigastric pain, nausea, poor appetite, attacks of weakness and nervousness is highly suggestive of atrophic gastritis, especially if additional

complaints of sore tongue and numbness or tingling in the limbs are present. I believe that chronic atrophic gastritis is a very serious disease. It may incapacitate its bearer and, since it may be the precursor of gastric carcinoma, as will be shown later, it must be considered and treated as a major disease. Laboratory findings are of minor importance. Anacidity was found in fourteen out of forty-two cases; two-thirds of the patients did not have anacidity. Occult blood is found sometimes, and in three cases gross gastric hemorrhage was noted, evidently caused by a small inflammatory erosion. Benign obstruction of the pylorus may occur.

Chronic hypertrophic gastritis is also a severe disease. Its symptoms are gastric symptoms highly suggestive of ulcer.[6] Night pain and delayed pain are frequent, but this pain often lasts only a few days; then the patient feels entirely well again; he quickly learns, however, that he must be careful with his diet to avoid a relapse. Gastroscopically one may see during an attack the gastric mucosa swollen with many scattered shallow gray erosions. A few days later all these erosions are gone but still some hypertrophic areas are seen. Complete cure seems to be rare. Gross hemorrhage as a complication has been observed by all gastroscopists. Fatal outcome is not rare. In some cases x-ray examination gives the picture of the so-called "cob-corn" or granulation relief picture. We found it in Chicago only twice in 300 cases. Flakes of mucus or remnants of food may simulate this picture of dark round holes. We have never succeeded in demonstrating by x-ray the definite localized alterations of the mucosa seen gastroscopically, such as single stiff folds or circumscribed node-formation.

We have seen that, with the exception of a few cases, gastroscopy is the sovereign diagnostic method for chronic gastritis.[7] Difficulties in the gastroscopic diagnosis of chronic gastritis, however, may be experienced also, especially in diffusely infiltrating forms, and the expert may face insurmountable difficulties. These cases, though rare, are important. In a thirty-five year old male the x-ray picture suggested carcinoma of the antrum, the gastroscopic picture was interpreted to be that of an ulcerative antrum gastritis. Through two years the picture remained essentially the same. Granular thickened mucosa with many ulcerations was observed. Finally, rather suddenly, atrophy of the antrum mucosa developed. One month later the patient developed fever and a retroperitoneal tumor. At operation a Hodgkin tumor was found; a biopsy was taken and a biopsy of the antrum was made. The excised stomach wall showed

Fig. 4 a

Fig. 4, a and b

Gastroscopic (a) and microscopic (b) picture of chronic hypertrophic gastritis. Gastroscopically the mucosa is irregular with "cobblestone formation". Microscopically tremendous proliferation with edema and infiltration is seen.

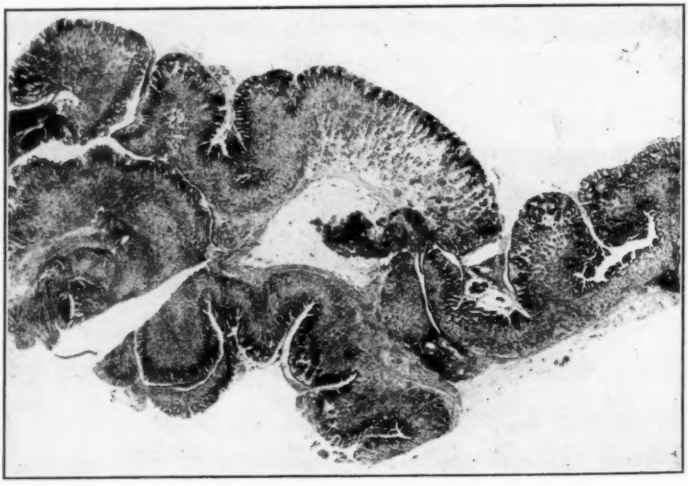

Fig. 4 b

the typical picture of atrophic gastritis as observed gastroscopically, but not the least sign of Hodgkin lymphogranuloma. In the case of a thirty-seven year old woman with anemia, x-ray suggested polyposis. She had been treated for a severe protein-deficiency state. One year later slight epigastric distress with vomiting developed. The gastroscopic picture was difficult to interpret; all types of diffuse infiltrations were considered. Pyloric obstruction led to immediate surgery, and in this case severe ulcerative antrum gastritis was present. The gross specimen showed

ulcers and inflammatory nodes. The microscopic section through the largest ulcer showed that it did not penetrate the muscularis mucosae. Cystic atrophic hyperplastic gastritis was seen. A section through the nodes revealed the inflammatory character.

Recently we observed three cases of tumor causing gastritis. I shall describe only one of them. A tumor was diagnosed by x-ray; gastroscopically an extensive hypertrophic gastritis had been diagnosed and a bulging in of the lesser curvature had been interpreted correctly as an inflammatory tumor. Laparotomy revealed unusual inflammatory changes of the entire interior of the stomach and of almost the entire small intestine as well. The folds reached a height of 2 to 3 inches. A biopsy was made. Microscopically a tremendous proliferation of the mucosa was observed, with edema, hemorrhage and infiltration by plasma cells, leukocytes, and eosinophils. The last case of this series of difficult gastroscopic diagnoses shows that the microscopic difficulties may not be less outspoken. In a sixty-three year old man, complaining of relatively mild epigastric distress with moderate weight loss, clinical, laboratory and x-ray examination revealed nothing. Gastroscopy showed tremendous bleeding, nodular infiltration of the entire posterior wall with many small ulcerations and atrophic areas. The diagnosis of a diffuse infiltrative lesion was made and laparotomy was advised. The surgeon was unable to feel anything pathological in the stomach; however, he made a biopsy, and microscopically a most unusual section was obtained. There was no unity among the pathologists in the interpretation of this section. The majority made the diagnosis of lymphoblastoma, but the diagnosis of an unusual form of chronic atrophic gastritis has also been made. This unique case must be watched carefully.

The therapy of chronic gastritis, as derived from gastroscopic observation, will be discussed very briefly. The variations in the picture of such a multicolor disease, of eminently chronic course with many spontaneous remissions, render the judgment of the effect of any type of therapy very difficult. In all its forms chronic gastritis should be considered and treated as an important disease. Possible etiologic factors, such as infected tonsils, sinusitis, alcoholism, nicotine, should be eliminated. A bland diet is always advisable. The mechanical work of the inflamed mucosa should be reduced as much as possible. Raw cellulose should be eliminated; spices should be avoided in the superficial and hypertrophic forms, but are sometimes recommendable in atrophic forms.

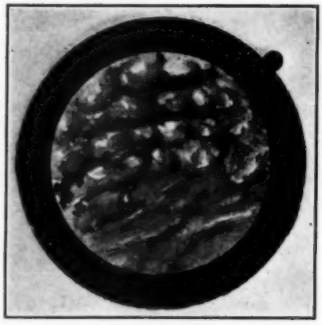

Fig. 5a

Fig. 5, a and b

Gastroscopic (a) and microscopic (b) picture of a rare case of "lymphoblastomic gastritis." These severe changes were found neither by most refined x-ray relief studies, nor palpated at surgical interference, but only at gastroscopic and microscopic examination. Gastroscopically infiltration with erosions and bleeding is seen. Microscopically the mucosa is destroyed by a dense infiltration of lymphocytes.

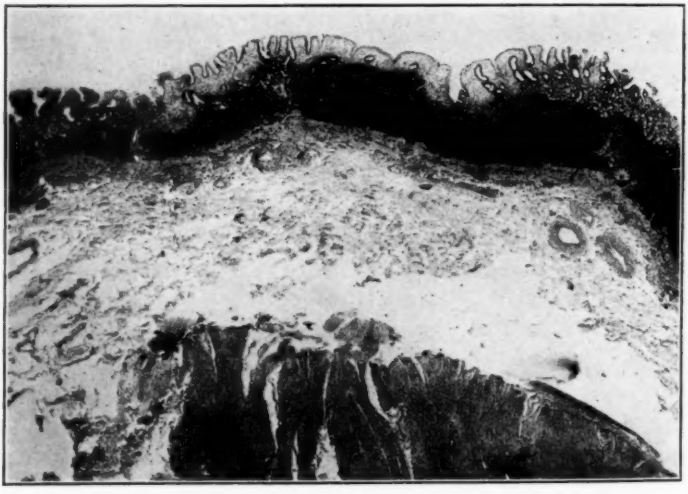

Fig. 5b

Frequent small meals may be given. If ulcerations are seen, one should insist on rest in bed for a few days with hot applications. Longer rest in bed may be necessary after a gross hemorrhage. In my opinion, gastric lavage is often very useful in superficial gastritis. Lavage is less valuable in the other forms. Alkalis may be agreeable in some cases of hypertrophic gastritis. In atrophic gastritis hydrochloric acid and charcoal sometimes are appreciated. In cases of atrophy in which deficiency states may be suspected, liver may be tried, iron or vitamins, especially nicotinic acid.

Three of our patients with atrophic gastritis responded definitely to liver injections by regeneration of the gastric mucosa. High voltage x-ray therapy was tried first in a case of ulcerative hypertrophic gastritis observed over a period of ten years. The success was amazing, but one year later severe atrophy developed as a late effect of the irradiation. Newer observations confirmed the effectiveness of this type of therapy; however, the end results are still unknown. Surgical treatment, in my opinion, is justified only in the rare cases of gastritic pyloric obstruction. Gastritic gross hemorrhage is a definite contraindication to gastric surgery.

I come to the last chapter, to the complications and sequelae of chronic gastritis. The activity of the bowels is not impaired in uncomplicated gastritis. If diarrhea is noted, inflammation of the intestine may be assumed. The Argentine workers, Royer, Bur, and Montejano,[8] found (gastroscopically) gastritis in one-third of their colitis cases. In a case diagnosed clinically as Crohn's disease, I found (gastroscopically) severe hemorrhagic ulcerative gastritis. Chronic cholangitis together with chronic gastritis has been found frequently. In such cases the aldehyde reaction usually is strongly positive. The lesion may be an ascending or a descending one. The latter type with fatal outcome was observed once by myself.

The close relation of gastric atrophy to pernicious anemia is well known. Knud Faber,[9] Hurst[10] and others believed that chronic gastritis is the primary disease destroying the function of the pyloric Brunner glands, a possible source of Castle's[11] antianemic factor. Chester Jones, Benedict and Hampton[2] were the first to observe that liver therapy leads to regeneration of the gastric mucosa. This observation, confirmed by Chevallier and Moutier[12] and Lehmann,[13] speaks, in my opinion, against the correctness of the mentioned theory. Gastroscopic observations in twenty-three cases of pernicious anemia[14] led to the conclusion that there must be a primary dysfunction of those cells which produce the antianemic factor, and a secondary degeneration of the gastric surface epithelium with following genuine inflammation.

Konjetzny,[15] whose extensive surgical and histological work is of the utmost importance, has contended that chronic gastroduodenal ulcer develops from chronic gastritis, and in reality is a gastritic ulceration. This gastritic theory of gastric ulcer is widely accepted in Europe. Konjetzny described a macroscopically visible ulcerative antrum gastritis

in 50 per cent of all cases of duodenal ulcer he operated upon, and microscopically visible changes in all cases. In American hospitals these changes were not observed, and Walters and Sebening[16] therefore assumed geographical differences. Our gastroscopic observations have failed entirely to confirm Konjetzny's statements. Gastritic ulcerations have not developed into gastric ulcer, and ulcerative antrum gastritis has not been found in cases of ulcer. The relation of gastritis to gastric ulcer as noted in ninety-one cases of gastric ulcer has been studied by Dr. Baxmeier of Pittsburgh and myself.[17] Our findings did not support the gastritis theory. In 47 per cent of all ulcer cases, no inflammation was found. We therefore had the idea that differences in surgical technique may be responsible for this discrepancy. Gastric resections and other gastric operations were carried out in twenty-two dogs by Dr. H. Necheles, Dr. R. Gold and myself[18] with the following results. If a simple resection is made, the resected specimen does not show any pathology. If we filled the dog's stomach with N/10 hydrochloric acid and quickly excised it two hours later, we again found a normal mucosa. But if we filled the stomach with hydrochloric acid of the same concentration and made a resection, a severe ulcerative hemorrhagic antrum gastritis was seen, sometimes proceeding to extensive destruction of the mucosa. If we ligated the arterial blood supply of the left side of the stomach and then cut the stomach out, nothing was seen; but if the operation was performed and hydrochloric acid was used, ulcerative gastritis exactly corresponding with Konjetzny's pictures[15] was found only in the areas without blood supply, sharply demarcated from the other side of the gastric wall. Microscopically we see that the vicinity of the ulcerations is full of plasma cells, an astonishingly rapid inflammatory tissue reaction, which is entirely absent at some distance from the ulcer. These experiments seem to support our gastroscopic observations and to prove that chronic gastritis and gastric ulcer are two different diseases.

Fortunately we are able to support fully Konjetzny's ideas[15] about the origin of gastric carcinoma. Rarely, if ever, carcinoma develops in a normal gastric mucosa. Gastroscopically, as well as microscopically, carcinoma develops in an inflamed mucosa, sometimes in several places, multicentrically. Gastroscopic observation and clinical check prove that frequently atrophic gastritis is a definite forerunner of gastric carcinoma, a precancerous condition.[1] I myself, in 1933, suggested periodical x-ray and gastroscopic examinations of patients suffering from atrophic gastritis

as the most important weapon in the fight against the most frequent carcinoma. Minimal gastric carcinomas cannot be found otherwise than incidentally, and they will be found incidentally if we decide to carry out periodic x-ray and gastroscopic examinations in patients suffering from atrophic gastritis. The last three case reports will confirm this statement.

A fifty-seven year old patient suffered for more than one year from mild epigastric distress. In the last few months he had some loss of weight. X-ray revealed a prepyloric ulcer. Because of the long case-history, the presence of hydrochloric acid and good response to ulcer therapy, the ulcer was considered to be benign. The gastroscopic picture, however, was that of an extremely small pyloric carcinoma. Atrophic gastritis was found around the lesion. After resection, grossly, no signs of malignancy were discovered; but, microscopically, in full accord with the gastroscopic picture, a minimal carcinoma was found. Its width was 8 mm., the depth 0.5 mm. to 2 mm. It is unbelievable that this small carcinoma could have produced symptoms of one year's duration. These symptoms probably were due to the existing atrophic gastritis which also was found microscopically; and probably the discovery of the minimal carcinoma was incidental and due to the careful x-ray and especially due to the gastroscopic examination.

A fifty-four year old surgeon suffered for more than ten years from epigastric distress. Severe purulent cholangitis was found at a cholecystectomy, but the distress was not relieved. The patient developed a histamine proved anacidity, and in the last eight years had terrible attacks of anorexia, weakness and exhaustion. Within the last three years a filling defect of the greater curvature developed. This was thought due to spasm. The defect grew slowly, and when the patient finally submitted himself to the gastroscopic examination, a polypoid tumor was found to lie in an entirely atrophic mucosa. This diagnosis would have been possible two years earlier by gastroscopy. However, the patient recovered after resection. A microscopic section through the edge of the tumor showed the mucosa to be completely atrophic, and the transformation of the atrophic mucosa into tumor tissue was observed. It is a typical case: chronic cholangitis, severe chronic atrophic gastritis of ten years duration, slow development of a carcinoma which by periodic gastroscopic examination would have been discovered at least two years earlier.

The last case shows that such incidental diagnoses are possible in

reality. A fifty-nine year old man suffered from pernicious anemia and combined cord degeneration. Our roentgenologists were unable to find any pathologic change. Only for the sake of completeness, gastroscopy was undertaken. In the antrum atrophic gastritis was seen, but in the midportion of the stomach toward the greater curvature the ulcerated wall of a small gastric carcinoma appeared. X-ray examination repeated with compression and relief films was negative, but at operation a very small adenocarcinoma was excised.

Knowledge of chronic gastritis is of outstanding importance in our fight against gastric cancer. The following points are the obvious results of these observations: 1. Superficial gastritis should be prevented from turning into atrophic gastritis by thorough treatment. Therefore it must be diagnosed gastroscopically. 2. Atrophic gastritis, the precancerous condition, should be diagnosed. This is also possible only gastroscopically. 3. If atrophic gastritis has been diagnosed, the patient should be observed, but naturally not told the reason for this observation. Every six months x-ray and gastroscopic examination should be undertaken. With such a program we may hope to discover carcinomas of minimal size and to bring about cures in a percentage of cases not dreamed of until now, as shown by the presentation of the last three cases. Chronic gastritis—a severe disease in itself—derives its most outstanding significance because of its role in the fight against gastric carcinoma.

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MODERN TREATMENT OF SCHIZOPHRENIA*

KARL M. BOWMAN

IN DISCUSSING the modern treatment of schizophrenia, I assume that this audience is composed mainly of physicians who are not psychiatrists and who are not experienced in the newer methods of treatment of this disorder. I shall therefore present briefly certain data concerning schizophrenia, its incidence, symptomatology and some of the theories as to its causation together with past methods of treatment. Following this, I shall discuss the newer methods of treatment, their techniques, the theories used to explain their value and the results obtained. Finally, I shall allow myself the luxury, and danger, of certain predictions.

Schizophrenia, or dementia praecox, represents one of the most important medical and social problems facing us at the present time. This disorder usually comes on during late adolescence or early adult life, has comparatively little effect on the life span of the individual, and until recently has shown very little response to any method of treatment. It is the most common type of mental disorder in our state hospitals. Approximately one-fifth of all admissions to state hospitals are cases of schizophrenia, and because it usually results in deterioration but does not shorten life, over one-half of the population of state hospitals is composed of such cases. Since hospitals for mental diseases have slightly more patients than do all other hospitals combined, including general hospitals, children's hospitals, maternity hospitals, and tuberculosis sanitaria, the result is that approximately one bed out of every four of all the hospitals in this country is occupied by a case of schizophrenia. Approximately thirty thousand new cases of schizophrenia are admitted every year to our state hospitals. It seems impossible, therefore, to exaggerate the importance of the study of schizophrenia from the standpoint of its prevalence, its cost to the community, and the amount of suffering which is caused.

Kraepelin gave the term "dementia praecox" to a group of mental disorders variously known as dementia simplex, catatonia, hebephrenia

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and paranoia. He felt that these disorders were to be grouped as a single disease and that all had in common certain qualities, particularly that they came on early in life and led to deterioration. Hence the name "dementia praecox." Bleuler, years later, suggested the term "schizophrenia," feeling that the term "dementia praecox" was a misnomer since, he claimed, all cases do not come on early in life and do not become deteriorated. He regarded the essence of the disorder as a splitting of the psyche, hence the term "schizophrenia." Bleuler likewise includes under schizophrenia a larger group of disorders than Kraepelin did under dementia praecox.

Here, already, we find one reason for difficulty in evaluating any method of treatment. Different clinics disagree in the criteria for diagnosing this disorder. This is particularly true concerning certain acute cases which recover spontaneously. The older Kraepelinians held that no case of dementia praecox completely recovered. If it did, the diagnosis was wrong. Some psychiatrists now insist that a considerable number of cases completely recover and that many more improve greatly with no particular treatment being given.

Almost every conceivable theory has been advanced to explain schizophrenia. Some feel that it arises essentially on an hereditary basis. Others feel that it is explained by some physical factor, such as a brain lesion, an endocrine or metabolic disorder, or an obscure toxemia from foci of infection from other parts of the body. Some feel that it is only to be understood on the basis of psychological factors and that certain repressions and mental conflicts are the actual cause. Finally, there are those who say that it is not a question of either/or, but rather a question of how much of each one of these factors; that is to say, there are a group of psychiatrists who feel that schizophrenia does not arise on the basis of a single cause, but that it is due to a number of causes, some of which may be hereditary, some of which may be organic, and some of which may be psychogenic.

As might be expected, the methods of treatment have depended upon the particular view the psychiatrist had concerning the cause of the disease. If the disease is purely hereditary in nature, it is obvious that the only satisfactory approach is through eugenics and that the disease can be stamped out only by ridding society of a certain stock which is the carrier of the disorder. The organic school has tried all conceivable types of remedies. Particular attention has been paid to the removal of foci of infection and the use of endocrine preparations. While there have been

some very optimistic reports of the results of such treatment, at the present time the general consensus of opinion is that we can produce comparatively little modification of the disorder by such methods of treatment. During the past two or three decades, there has been great emphasis on the psychological treatment, and such attempts have received support partly because other methods of treatment seemed of little or no avail. The use of re-education and occupational therapy has become an important part of the treatment of these cases in all of our best institutions, and has demonstrated that it was of value, although no one has considered it as a panacea. The use of hypnotism, psychoanalysis, and various types of psychotherapy has accomplished, on the whole, comparatively little, although there are those who feel that such methods are extremely valuable and have accomplished more than any other type of therapy that has been used.

While psychotherapy, occupational therapy and the general management and re-education of the patient represent important recent advances in the treatment of schizophrenia and other mental disorders, I shall devote the rest of this paper to certain physiological methods. These can best be grouped under fever therapy, sleep therapy and stimulation therapy.

For many years fever therapy was developed at the Vienna Clinic under Wagner Jauregg. He was able to cure some patients suffering from syphilis of the nervous system and improve many others by inoculating them with malaria. Many other methods of producing fever were developed such as the use of diathermy, hot air cabinets, hot baths, injections of typhoid vaccine, and inoculation with rat-bite fever. These various methods have been tried out extensively in cases of schizophrenia but, in general, the results have been unsatisfactory. The production of aseptic meningitis is another example of the numerous attempts of this sort.

Sleep therapy is commonly regarded as a recent method, yet we find that Dr. John C. Warren of Boston used ether as early as 1847. Later he used cannabis indica, known to us now under the name of marihuana. Opium had been used for mental conditions for many centuries. Various authors reported improvement from different types of sleep therapy, but in 1922 Klaesi reported excellent results from prolonged narcosis due to somnifen. Other clinics took up the treatment by prolonged narcosis and other drugs such as hyoscine and luminal were used extensively. Somnifen was held by many to be unsafe and its use has been

largely discontinued. Sodium amytal, however, has proven itself of definite value and is being used at the present time in a number of clinics throughout the country. The effects of this drug are particularly striking in catatonic stupors, certain cases showing remarkable improvement. It is difficult to say if this should be regarded as sleep therapy as the immediate result is the disappearance of the stupor so that the patient becomes alert and clear.

Various types of stimulating therapy have also been employed and it is of interest to point out that Henry Hurd used monobromate of camphor in 1885 and even produced convulsions in some patients. Sodium cyanide, a respiratory stimulant, was first used by Lowenhart in 1918 for cases of stupor. He was able to produce temporary improvement in some cases, and a number of patients who had been mute would talk following such treatment. Later, carbon dioxide inhalations were used as a form of stimulating therapy. Patients would breathe a mixture of carbon dioxide and oxygen, and many stuporous patients could be temporarily brought out of their stupor by this treatment. However, little in the way of lasting cures was produced by such treatment, and some psychiatrists felt that the greatest value of carbon dioxide was to enable the psychiatrist to secure contact with the patient during his temporary improved spells, and that by means of the psychotherapy which could then be extended, the real possibility of successful treatment occurred.

Gradually, therefore, during the last twenty years, new methods of physiologic treatment have been evolved and gradually the feeling has arisen that we were beginning to develop physiological methods of affecting the schizophrenic process.

Recently, the use of two new drugs, insulin and metrazol, has given us still better methods of treatment. For a number of years, insulin in small doses has been used for the treatment of various mental disorders, including schizophrenia. It was felt that patients showed physical improvement, their appetite improved and they gained weight. Some showed mental improvement. Occasionally, a patient received an unusually large dose of insulin and went into shock or coma. Interestingly enough, several observers reported that patients seemed improved following this large dose of insulin, but none of them followed up this observation or seemed to draw the conclusion that it would be desirable to give large doses of insulin in the treatment of schizophrenia. Sakel first made use of insulin as a means of treating morphine addicts. He noted

that it had a quieting effect upon them, and felt that this was due to some effect that it produced on the vegetative nervous system. Sakel then felt that insulin might be of value in quieting disturbed psychotic patients, and experimented with it. Moreover, when noting the improvement that seemed to follow shock or coma produced accidently, he decided that there was definite value from this treatment and continued to experiment with shock doses of insulin. He did not feel that the treatment was specific, but rather that the pharmacological shock affected the various vegetative centers and brought about a restoration of normal physiological function. Sakel published a number of articles on this subject in 1933-34-35. These articles were combined in book form, and recently this book has been translated into English.

As might be expected, Sakel has modified both his theories and his technique of treatment as he has gained more knowledge and experience. The essence of the treatment was that patients were given daily sufficient insulin to produce shock or coma. After a variable number of treatments, some of these patients either improved or appeared to recover completely. Originally, Sakel talked of convulsion therapy and deliberately sought to induce convulsion in some cases. However, after a certain amount of experience, it appeared that the patients who went into coma seemed to do better than those who developed convulsions, and for a period of time, emphasis was placed on the value of producing a coma and the dangers from the convulsion were probably exaggerated. More recently, and with added experience in treating cases, a more individual type of technique has been developed and the value of one type of shock for certain cases and another type of shock for other cases has been clearly recognized. As would be expected, the technique of the treatment has been built up largely by trial and error. This is said not in any criticism, since it was the only possible way that our present knowledge could be attained. In addition to using insulin, Sakel has again returned to the use of metrazol and has worked out several new techniques for the combined treatment.

Sakel originally divided the insulin treatment into four phases. In the first phase the patient was given daily injections of insulin, starting with 10 to 30 units and increasing the dose daily until the patient developed shock or coma. The insulin was injected intramuscularly early in the morning and the patient would have had nothing to eat since the night before. Food was given about four or four and one-half hours after

the insulin injection. Phase two began when the dosage was sufficient to produce severe hypoglycemic shocks. These shocks might be either coma or convulsions. In the development of the hypoglycemic coma the patient would perspire profusely, might have spells of excitement, but would gradually become sleepy and go into coma. This would occur, ordinarily, about four hours after the injection of insulin. A typical coma of this type was called the wet shock. Certain cases, however, would develop during the second or third hour a typical epileptiform convulsion and would not have the profuse perspiration described in the wet shock. Sakel referred to this condition as dry shock. He also pointed out that there might occur a late epileptiform convulsion during the fourth or fifth hour of hypoglycemia and that this might occur with a typical wet shock. Sakel felt that the late epileptiform convulsion was a danger sign and that steps should be taken immediately to terminate the coma. A typical dry shock, however, he felt was in some cases desirable and that attempts should be made to induce it, whereas the late convulsion was regarded as undesirable. In both cases it was felt that the convulsion was the sign for the termination of treatment. Phase two was to be continued from twenty to fifty days. Phase three was the term that Sakel applied to a period of rest days which he felt necessary to introduce from time to time. At present less emphasis is placed on this phase. Phase four was a period of about one week during which the patient was given reduced doses of insulin, and carbohydrates were administered within two hours after the injection. Sakel originally felt that it was important to taper off treatment in this fashion, but he now feels that in many cases it is not necessary.

The essence of the treatment, aside from the technique mentioned, is the development of the proper type of shock and the termination of the shock at the proper time. When it was desirable to produce wet shock, that is, coma, Sakel felt that if necessary drugs such as barbiturates might be utilized to minimize the chance of convulsions developing. He also stated that if all external stimuli were kept out and the room was darkened and quiet, the patient was less likely to develop convulsions. It was noted that there was a certain critical period in the second and third hours when the patient would most easily develop convulsions. If, on the other hand, it was decided to produce convulsions, various measures might be resorted to, such as having the patient in a state of alkalosis, having the patient drink large amounts of water and exposing the patient to external

stimuli during the second and third hours. Furthermore, one might even give such drugs as camphor and metrazol at this time in order that such a convulsion might be produced. The matter of the proper timing of the hypoglycemic state was difficult to decide and could not be settled arbitrarily for an individual case. Early in the development of the treatment Sakel felt that cases of catatonic excitement should be given two or three injections daily, starting with 15 to 20 units, approximately. As soon as the patient responded to insulin by becoming quiet, he was given food. Later, as the procedure developed, treatment was terminated just before the patient went into coma. The treatment for stupor was somewhat similar in principle. In general, sugar was given fairly early. In some cases dry shock was deliberately encouraged. For paranoid cases, Sakel felt that protracted wet comas were the best treatment. However, he stressed the necessity of individualizing and the point that in every case one must determine how the patient reacted to a particular type of treatment and continue accordingly. In general, therefore, one started out with the regular type of treatment, varying it from time to time, and noted how the patient responded to these variations. Accordingly, if the patient responded well to a long, wet coma such treatment would be continued. If he responded satisfactorily to a dry shock, this was continued. Sakel has continued to emphasize this necessity of individualizing the treatment, and all attempts to lay down set rules of treatment have proven unsatisfactory.

The method by which hypoglycemia is terminated depends on the condition of the patient. If able to swallow, the patient may drink sugar water. The general plan is to give a 40 per cent solution of sucrose in warm water. The number of grams of sugar should equal the number of units of insulin plus 10 per cent, so that if the patient received 100 units of insulin, he would be given 110 grams of sugar. If the patient is unable to swallow, the common method of terminating coma is to pass a stomach tube intranasally and thus secure absorption through the gastrointestinal tract. A little atropine may be given to prevent vomiting and spasm. In a case where immediate termination is necessary, glucose solution may be given intravenously. It is important to remember that further sugar should be given in such cases as soon as the patient wakes up; otherwise he is likely to return again to coma.

The maximum period for hypoglycemia should be six to seven hours. Certain dangers may be mentioned. With the abolition of the reflexes,

great care must be taken that the stomach tube is actually in the stomach. Sakel discusses a special technique for determining this. The second danger is aspiration during coma. With the marked increase of salivation and the absence of reflexes, the patient may easily aspirate material into the lungs. The patient, therefore, should be placed in a position which will prevent this from occurring. A third danger is spasm of different muscles. There may be spasm of the vocal cords or of the pylorus of the stomach. A fourth danger is that the patient may become chilled due to the excessive perspiration and the decreased heat production. This may be guarded against by the use of blankets and of hot water bottles, if necessary. Fifth, it should be kept in mind that there are many individual differences in the reaction to insulin, and that on rare occasions patients may get a severe reaction to a small dose of insulin, yet no reaction to a large dose of insulin. John reports one case in which an increase of 2 units of insulin in an adult produced a violent reaction, and another case in which a five-year-old child was given 100 units of insulin intravenously twice a day for a whole month with no reaction occurring.

I have related very briefly how Sakel came to use insulin shock for the treatment of schizophrenia. Space does not permit a discussion of his earlier theories or a detailed critical analysis of his more recent formulations. It is obvious that much of the work with insulin was started and carried along on an empirical basis but that, having found a method of value, attempts have been made to explain why it produces these results. Sakel has published numerous articles on the subject in which he has attempted to give a theoretical explanation for this method of therapy. However, one must admit quite frankly that Sakel's theories as to how insulin benefits schizophrenia are much less impressive and satisfactory than his actual treatment. Sakel himself has admitted dissatisfaction with his own theories and has continued from time to time to revise them. Quite simply, Sakel's theory might be summed up as follows: In schizophrenia new patterns of behavior of an unhealthy nature have been acquired. Insulin shock temporarily places the brain at rest and has some effect in obliterating these newly acquired neural pathways. When the nervous impulses are blocked from flowing over these newer and abnormal pathways, they revert to the older, normal pathways; this causes normal behavior, or a return to the prepsychotic personality. Further discussion of the theoretical considerations of insulin treatment will be given later.

The use of metrazol alone as a specific method of therapy for schizophrenia was introduced by Meduna who had been greatly interested in a number of observations by various writers that epilepsy rarely occurred in schizophrenia, and that in some way epilepsy prevented the development of schizophrenia. The following is his own formulation of this hypothesis: "Between epilepsy and schizophrenia there is a biological antagonism. Should it be possible to induce epileptic attacks in schizophrenic patients, such epileptic attacks would change the chemical, humoral, haematological and other aspects of the organism in such a manner that thereby—since the organism so changed would represent an unfavorable basis for the development of schizophrenia—a biological possibility is given for a remission of the disease."

After trying various drugs he used camphor which he felt was of value, but soon switched to metrazol which he felt was much more satisfactory. Briefly, the essence of metrazol treatment is that the patient receives intravenous injection of 5 cc. of 10 per cent solution of metrazol. The exact dosage varies for individual patients and must be determined by experimentation in the case of each patient. The injection is given as rapidly as possible, since if it is given slowly no convulsion is produced. Within a few seconds following the intravenous injection of metrazol, the patient develops a very typical epileptic convulsion. There may be one or two preliminary twitches, sometimes a cry occurs, and the patient then goes into a tonic state which is followed shortly afterwards by a clonic state. The pupils are usually dilated, do not react to light, and Babinski's sign is positive at the end of the clonic phase. Following the attack, the patients are usually confused and often fall asleep; this confusion usually disappears largely at the end of five to ten minutes. The technique of treatment consists in the production of two or three such convulsions a week for a period of three to ten weeks. The length of treatment depends upon the patient's response, some cases clearing up rapidly and other cases failing to show any response whatsoever.

It will be seen, therefore, that Meduna's concept as to the basis for using metrazol is quite different from Sakel's theoretical basis for using insulin. Actually, however, in patients under treatment with insulin, metrazol convulsions are sometimes induced.

Sakel originally used drugs including metrazol to produce a dry shock or convulsion, and others, working in this field, advocated the use of metrazol to produce a convulsion during the second or third hour just

about the time the patient is going into coma. This combined treatment has been used for some time in a number of clinics and is felt to be of value in certain cases, particularly those not responding well to insulin.

Quite recently Sakel has developed a further modification of the combined insulin-metrazol treatment which he regards as of especial value in treating chronic cases and cases which do not respond to other methods of treatment. I quote Sakel's own words in describing this technique: "In cases which have been unaffected by other methods, a protracted or a so-called condensed shock has often proved efficacious. The condensed protracted shock consists of provoking a convulsion in a comatose patient with a small dose of metrazol during the fourth hour of the coma, when he is just on the verge of a late convulsion. The patient then wakes spontaneously and, if desired, may even be left two hours longer in coma. The fact that I have effected improvements just as easily in patients who have only undergone the treatment two or three times, as in those who have been treated over an extended period, points to the conclusion that an amnesia for the psychosis, figuratively speaking, is produced. Physiologically expressed, this means that in such cases we deliberately produce slight injuries to the brain cells, and, by destroying the dominating pathological cells, we assist the dominating healthy cells to break through between those sections which have been producing the psychotic personality."

To understand what common factor there may be in both insulin coma and metrazol convulsions, let us turn for a moment to the study of brain physiology. As is known, the brain metabolizes only carbohydrates, although small amounts of lactic acid and alcohol may also be utilized. In insulin coma the carbohydrates in the blood stream are greatly reduced and studies which we have made at Bellevue show that very little oxygen has been taken out of the blood circulating through the brain. In studying contents of the blood samples of the internal jugular vein and femoral artery, we have shown that there was a fall in the utilization of oxygen of approximately 65 per cent. This indicates that the brain is put at rest by a lack of carbohydrates, although there is an adequate amount of oxygen in the blood. In the metrazol convulsion, the brain is likewise put at rest, but in a different fashion. The oxygen supply to the brain is cut off although the carbohydrate supply in the blood is quite ample.

As a result of studies at Bellevue, the following theoretical considerations have been formulated:

"Insulin hypoglycemia depresses cerebral metabolism by diminishing the food supply of the brain (blood sugar), while metrazol achieves the same effect by decreasing the oxygen available for the combustion of this foodstuff. Thus, insulin therapy affects the brain specially, for that organ utilizes carbohydrates chiefly, while metrazol has a generalized effect on all the organs of the body including the brain. The effect of insulin on the brain is more prolonged, while that of metrazol is more severe. However, in both cases the depression of cerebral metabolism seems to favor the amelioration of schizophrenia."

How valuable are these newer methods of treatment? One can hardly go over the different statistics from the various countries, but in general it may be stated that the large majority of clinics using insulin treatment are convinced of its value, and there is a striking agreement in statistics from these different clinics. The chances of cure depend definitely on the length of time the patient has been sick. Cases of less than six months' duration have much the best recovery rate. This high recovery rate, with some reduction, continues up until about eighteen months, after which there is a marked decrease in the percentage of cures. Many clinics report a recovery rate of from 60 to 70 per cent in cases of less than six months' duration, with improvement in 10 to 15 per cent more. Here, of course, there is room for much argument; first, as to the definite diagnosis of schizophrenia in an early case, and second, as to what constitutes recovery. It can hardly be expected that one is going to make an ideal personality out of a schizophrenic patient who has been treated, and we speak of cures in the same way that we would refer to them with relation to physical disease. In speaking of them, then, we do not assume that the individual has been made over into a perfect specimen physically. Even in most physical disease, when we claim a cure, there are probably some residues; a patient who has had pneumonia may never completely recover so that his lungs are as good as they were before the attack. In fact I believe it is generally assumed that a patient who has had one attack of pneumonia is more likely to have further attacks than is a person who has never had an attack. Yet certainly we speak of such patients as cures, and in the same sense we may use the term cure in discussing the treatment of schizophrenia. A very excellent set of statistics is available from the New York State Hospitals which have now treated over 1,000 cases of schizophrenia by insulin and over 500 cases by means of metrazol. The lumping together of these cases from a number of different hospitals gives us

a good idea of what may be expected by the use of these methods. These figures, while less optimistic than those of some clinics, give clear proof of the value of the two methods of treatment. It also seems to confirm the general impression given by statistics, that the insulin treatment has a slightly higher percentage of recovery to its credit than has metrazol. As to the practical value of these statistics, it would seem that we now have methods of treating schizophrenia which are of great value. However, the possibility of cure is greatly influenced by the duration of the disease. This indicates that we shall probably go through somewhat the same stages in dealing with schizophrenia that we have gone through in treating tuberculosis. There must be a campaign to educate not only the medical profession, but also the general public to the idea that schizophrenia is not a hopeless disorder, and that if diagnosed in the incipient stage, the majority of cases will respond to treatment.

The literature on this subject has become so voluminous that it is impossible to give any complete review of it. It may be pointed out, however, that there are reports from a great many different countries as to the value of the newer method of treatment and that in May, 1937, the Swiss Psychiatric Association held a meeting, the title of which was: "The Treatment of Schizophrenia—Insulin Shock, Cardiazol, Sleep Treatment." Dr. M. Mueller, who had previously reported one and a half years before on the use of insulin, discussed the further reports stating: "On the whole, however, there is a surprising unanimity as to the actual progress made with the help of the insulin treatment. This is particularly astounding, if we keep in mind that agreements on new methods of treatment have not been very common in our profession. Moreover, in checking the different remission rates, we find that the percentage of discharged patients, whose psychosis was of recent onset, varies between 50 and 80. Compared to this, there are some recent statistics showing that the remission rates for cases of similar duration of illness amount only to 30 per cent." He further states: "On the other hand, we must not forget how elusive are the clinical features of the genuine schizophrenia. Although such an eminent authority as Bleuler has paid special attention to this problem, we are still inadequately enlightened as to which elements in the picture of schizophrenia should be referred to the fundamental schizophrenic process and which should be regarded as pathoplastic phenomena or 'superstructure.' In their concept of what is essential in the true schizophrenia, different schools and different coun-

tries are widely divergent. I need only remind you of the work of Kleist and the departure of the French and Dutch schools from our Swiss idea of schizophrenia."

Sakel, at this same meeting, states as follows: "The therapy dates back to 1928. It is an outgrowth of observations made by me in the course of the attempted treatment of morphine addicts. I thought, first of all, that insulin abolished the phenomena of irritation during abstinence from morphine because the nerve cells were blocked and their function quantitatively affected." Sakel relates that he first ascribed the therapeutic effect of hypoglycemia to "cell shock." Sakel then states that he first thought the epileptic seizure was of great value, that he tried strychnine, adjustment in water balance, and the administration of camphor and of metrazol to produce seizures. He adds: "In the course of years I have, in most cases, abandoned supplementary medication aimed to provoke epileptic attacks. With time I have gained the impression that hypoglycemia as such, and nothing else, acts on the psychoses, while the epileptic attack prepares the way by unlocking the gates and altering the psychotic picture." Sakel further discusses his hypothesis, comparing the nerve cell to a combustion engine and the necessity of keeping up the working capacity of the nerve cell by a proper amount of food. The idea, therefore, is that insulin produces a diminution of the action of the nerve cell. The psychic changes during and after hypoglycemia are explained as follows: "I look upon a reaction of the nervous system as a response to stimuli, traversing certain pathways. Then the processes in hypoglycemia may be explained by a blocking of pathways previously active so that reactions to the same stimuli run their course over pathways previously inactive. . . . Now experience teaches us that the newest and most active organs as well as the most recently acquired pathways are most susceptible to injuries. When a nerve cell is injured the pathological change may be qualitative or quantitative."

Two other questions will immediately arise. What are the dangers of this method of treatment, and what are chances of relapse occurring. When treatment is carried out by well-trained individuals the danger is comparatively slight. The mortality rate in our best clinics has been shown to be, I believe, less than 1 per cent. At Bellevue where we have been carrying out treatment for nearly two and a half years, we have not yet a single fatality. Obviously, if persons past middle age are subjected to this treatment, there is considerably more risk than there would be in

younger persons. Cases of high blood pressure or cardiac disease are also poor risks, and can only be treated if this fact is clearly understood. The United States Veterans' Bureau, where most of the psychiatric patients are now over forty years of age, reports fairly encouraging results following the use of these two methods of treatment; results, which considering all the adverse circumstances, are sufficiently optimistic to make those who have treated such cases eager to continue doing so.

Fractures and dislocations occur at times as a result of the convulsive seizures. A recent report of compression fractures of the bodies of the lower dorsal vertebrae deserves further study. It is stated that most of these fractures are asymptomatic and will only be discovered by careful X-ray studies. Attempts are being made to prevent such fractures by putting the patient in extreme flexion or using some type of body cast or brace. It should be emphasized, therefore, that the use of insulin or metrazol is not a simple procedure to be carried out indiscriminately by untrained persons. Rather it should be regarded as one does a surgical operation. It is not without danger but the possibility of curing or improving patients who would otherwise never recover, justifies the risks taken.

Concerning the question of permanence of cure, it is still too early to make any positive statements. We know that a certain number of cases do relapse, but many times such cases respond favorably to a second course of treatment. In studying our own cases that relapsed following insulin treatment, we have been struck by the fact that many of them were cases who had comparatively little treatment. In the beginning we were, naturally, very conservative, probably too much so, and the result was that in these earlier cases when the person seemed to be responding well we terminated treatment and returned the patient to the community much sooner than we would now do. I feel, therefore, that a number of relapses are due to improper or inadequate treatment and that as time goes on our technique will have improved so that we will have fewer such relapses. A second point, which to me is of great interest, is that a number of cases that we have discharged as only slightly improved, have continued to improve after return to the community so that some of them, after six months or a year, are now put down as cures. This is a very hopeful sign and a result which we had not anticipated in the beginning, and is worth calling to your attention. The fact that there is still a chance for improvement or even cure in a patient who has re-

sponded only slightly to thorough treatment should make us all take a more hopeful attitude in returning these cases to the community. As to what will happen to patients many years after treatment, we cannot, of course, say at this time. However, even if a patient who was regarded as a cure were to relapse after a number of years, it might still be said that the treatment had been worth while and of definite value.

What should be most emphasized is that the use of insulin and metrazol has given us a weapon which enables us to attack and treat successfully in a relatively high percentage of cases, a disease which up to now has responded very little to any method of treatment. A study of the effect of this treatment should help us to get some idea concerning the nature of this unknown disorder which we label schizophrenia or dementia praecox. Personally, I doubt if either insulin or metrazol will remain with us long as the best method of treatment. I believe that we shall soon gain such a knowledge of this disorder that we will perfect still better methods of treatment. In this connection it is of interest that, while working with us at Bellevue on the study of the physiological changes produced by insulin and metrazol, Himwich was convinced that a simpler and better method of treatment could be formulated. If the deprivation of energy to the brain resulting from both insulin and metrazol treatment was the cause of the improvement, he felt that a simpler method of producing the same result might be worked out. As a result, an attempt was made to produce a similar type of response by having a patient breathe pure nitrogen, using an ordinary anesthesia mask with soda lime for removing carbon dioxide; the patient was allowed to go into a state of acute anoxia until he became unconscious and developed slight convulsive twitchings. Pure oxygen was then switched on and the patient quickly regained consciousness. Interestingly enough, the patient had no sense of suffocation and claimed that the treatment was not unpleasant; he also stated that he felt somewhat better as a result of the treatment. A personal communication from Himwich informs me that he has now treated four cases by this method and all four show a full remission. In this therapy the patient is subjected to three such treatments a week, thus resembling metrazol in the number of treatments given and also in the acute anoxia produced.

It would seem, therefore, from what I have presented this afternoon, that we have developed two methods of great value for treating one of the most common types of mental disorder which heretofore responded

but little to any type of therapy. Indications are that we will continue to improve our methods of therapy, that we will gain a further understanding of the nature of this disorder and that we may even achieve a method of prevention. At the present moment, I emphasize the point that we should not regard these conditions as hopeless and that the general practitioner has a definite responsibility with regard to the early diagnosis of such disorders and for seeing that treatment is instituted at the earliest possible moment, since it is clearly established that every day of delay in the starting of treatment definitely decreases the patient's chance of recovery.

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DEATHS OF FELLOWS

MEYER, MONROE ABRAHAM: 57 West 57 Street, New York City; born in New York City, August 1, 1892; died in New York City February 27, 1939; graduated in medicine from Cornell University Medical College in 1916; elected a Fellow of the Academy November 6, 1930.

Dr. Meyer was a Fellow of the American Medical Association and a member of the American Psychoanalytic Association, the American Psychiatric Association, the American Psychopathological Association, and the County and State Medical Societies.

PARRY, ANGENETTE: Huntington, Long Island, New York; born in Rome, New York, October 5, 1857; died in Boston, Massachusetts, March 1, 1939; graduated in medicine from the Woman's Medical College of the New York Infirmary for Women and Children in 1891; elected a Fellow of the Academy December 6, 1894.

Dr. Parry served as a member of the Executive Board of the American Women's Hospitals since its inception in 1917. She was a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, a member of the American Medical Women's Association and one of its former presidents, a member of the Women's Medical Society of New York State and one of its former presidents, and a member of the State and County Medical Societies.

Dr. Parry spent four years as one of its volunteers at the Kokkinia Refugee Hospital at Kokkinia, Greece. For her work there she received a decoration from the Government of Greece.

VOISLAWSKY, ANTONIE PHINEAS: 33 East 68 Street, New York City; born in New York City, June 5, 1872; died in New York City, February 22, 1939; received the degree of Bachelor of Science from New York University in 1894; graduated in medicine from Dartmouth Medical College in 1897; elected a Fellow of the Academy May 7, 1903; designated a Fellow in Otolaryngology in 1933.

At the time of his death, Dr. Voislawsky was chief of clinic and attending rhinologist and otolaryngologist to the St. Luke's Hospital, consulting otologist, rhinologist and laryngologist to the Harlem Eye and Ear Hospital, the Staten Island Hospital and the Northern Westchester Hospital, and consulting rhinologist and laryngologist to the Ruptured and Crippled Hospital and the Flower-Fifth Avenue Hospital.

Dr. Voislawsky, who was awarded a certificate from the American Board of Otolaryngology, was a Fellow of the American College of Surgeons, the American Medical Association, and a member of the American Laryngological Association, the American Laryngological, Rhinological and Otological Society, the American Otological Society and the County and State Medical Societies. He was a director of the Alumni Federation of New York University, and was at one time president of the Society of Alumni of St. Luke's Hospital. During the World War, Dr. Voislawsky served on the Medical Advisory Board of the Secret Service.